UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, Plaintiff, v. PHILIP MORRIS USA INC., f/k/a PHILIP MORRIS INC., *et al.*, Defendants.	Civil No. 99-CV-02496 (GK) Next scheduled court appearance: September 21, 2004

UNITED STATES' WRITTEN DIRECT EXAMINATION OF

DR. JONATHAN M. SAMET

VOLUME I

Q: Please state your name.

A: My name is Jonathan Michael Samet.

Q: Doctor Samet, are you a physician and an epidemiologist?

A: Yes.

Q: Are you licensed to practice medicine?

A: Yes. I am licensed in Maryland and New Mexico.

Q: What is epidemiology?

A: Epidemiology is a set of scientific methods used to track the health of populations, to identify the causes of disease in populations, and to intervene to improve the health of populations. Observational epidemiological studies involve assessing the consequences of exposures to people as they occur naturally and their results are consequently very important to society.

Q: Doctor, you are currently Professor and Chair of the Department of Epidemiology of the Johns Hopkins Bloomberg School of Public Health. Do you hold any other appointments at Johns Hopkins?

A: Yes. In addition to being chair of the Department of Epidemiology, I also hold appointments in the Oncology Center of the School of Medicine and in the Department of Medicine, and I am the Director of the Institute for Global Tobacco Control. I am also Co-Director of the Risk Sciences and Public Policy Institute.

Q: Please briefly describe the Johns Hopkins Bloomberg School of Public Health for the Court?

A: The School of Public Health, which is located in Baltimore, is the oldest school of public health in the United States, and at the moment the world's largest school of public health. I have

been at the School of Public Health since 1994, teaching a variety of subjects in epidemiology, some on the methods of the field itself, an introduction to epidemiology, and more advanced methods. I also give classes on cancer epidemiology, occupational epidemiology, environmental factors, epidemiology and public policy, clinical research and other matters. I have also remained active as a researcher since coming to Johns Hopkins.

Q: What are some of the administrative responsibilities that you have in the epidemiology department?

A: I deal with a broad range of administrative matters related to education, research, and personnel. We have a large department and very diverse research activities going on throughout the world. There are major programs on infectious diseases in Africa, Thailand, and Baltimore, studying, among other things, HIV infection and AIDS. We have large programs on cardiovascular disease, on respiratory diseases, on cancer, on clinical trials, on sleep disorders, and many other public health and clinical problems. The department has about 80 full-time faculty at present.

Q: Directing your attention to your educational background, what degrees do you have and from what institutions did you receive them?

A: I received my bachelor of arts in physics and chemistry at Harvard in 1966. I received a medical degree from the University of Rochester in 1970. And, I received a master's of science in epidemiology from the Harvard School of Public Health in 1977.

Q: Following graduation from medical school, where was your internship?

A: I interned at the University of Kentucky in internal medicine from 1970 to 1971.

Q: In that internship, did you have experience treating patients with lung cancer and chronic obstructive pulmonary disease, COPD?

A: Yes, extensive experience with treating lung cancer and I took care of many patients with COPD as well. At that time COPD was more commonly referred to as emphysema or chronic bronchitis and it was already very frequent.

Q: From 1971 to 1973, were you in the armed services?

A: Yes. I was a physician in the United States Army stationed in the Panama Canal Zone. I was an anesthesiologist at Gorgas Hospital, a 450-bed hospital.

Q: Did you complete your internal medicine residency?

A: Yes, I did, at the University of New Mexico in 1975.

Q: What patient care, if any, did you perform during your residency?

A: I treated patients with lung cancer, COPD, heart disease, and many other cancers. I treated many other types of disease as well.

Q: After your residency at the University of New Mexico, where did you continue your education?

A: From 1975 to 1978, I was in a fellowship at Harvard Medical School. As I already testified, I obtained a masters of science in epidemiology from the Harvard School of Public Health in 1977.

Q: Did you develop a medical sub-specialty?

A: Yes, in pulmonary disease.

Q: Did you work at any hospitals in Boston?

A: Yes, I treated patients at three hospitals: the Peter Bent Brigham Hospital, Massachusetts General Hospital, and Boston City Hospital.

Q: What were some of the diseases that you treated at these hospitals?

A: I treated patients with lung cancer, COPD, other cancers and many other diseases.

Q: When did you pass your internal medicine board examination?

A: In 1975.

Q: When did you pass your pulmonary disease subspecialty board examination?

A: In 1980.

Q: Are your board certifications current?

A: Yes.

Q: Was Dr. Frank Speizer one of your professors at the Harvard Medical School?

A: That's right. He was the director of my fellowship and a mentor. Dr. Speizer trained in epidemiology with Sir Richard Doll.

Q: Who is Sir Richard Doll?

A: Richard Doll has long been one of the field's preeminent epidemiologists. He did much of the pioneering work on cigarette smoking and diseases beginning in the late 1940s extending into the 1950s and remarkably to the present day. I'll be describing some of the findings of his work, particularly with regard to the well known follow-up study or cohort study that he conducted of about 34,000 male and 6,000 female British Doctors.

Q: Did Dr. Speizer start any similar studies?

A: Yes. He started the Nurses' Health Study, a very well-known follow-up study of over 100,000 U.S. nurses. It's a very important and well-regarded study of the effects of smoking and other factors on health. Dr. Speizer has won several prestigious awards including the Ochsner Award for research contributions to the study of smoking and health and he shared the Mott Prize, given by the General Motors Cancer Foundation, with Walter Willett.

Q: Did you do any original research regarding smoking and disease with Dr. Speizer?

A: Yes, during my years in Boston and subsequently.

Q: Returning to your experience as a teacher and as a clinician, when did you receive an appointment at the University of New Mexico School of Medicine in the Department of Medicine?

A: In 1978.

Q: What were your responsibilities?

A: Patient care in pulmonary and critical care medicine and in general internal medicine, training and research. Some of the patients that I treated had lung cancer; others had COPD and other types of cancer as well as many other diseases.

Q: At that time, what pulmonary health care did you provide?

A: I had a weekly pulmonary clinic. I also provided consultation and in-hospital pulmonary care. Periodically one of my duties was to supervise a team providing general medical care. When I became chief of pulmonary medicine my duties changed somewhat.

Q: When did you become chief of pulmonary medicine?

A: In 1986.

Q: What were your responsibilities as chief of pulmonary medicine at the University of New Mexico Department of Medicine from 1986 through 1994?

A: I carried out a broad set of administrative duties, some related to clinical activities and others to educational and faculty issues.

Q: In 1994, you left the University of New Mexico for Johns Hopkins; is that correct?

A: Correct.

Q: What kinds of clinical experience have you had other than what you have already described for the Court?

A: Over my years of being a physician I have had diverse experiences. As a resident at the University of New Mexico I took care of patients discharged from the University Hospital to nursing homes. Also over the years, particularly early in my career, I had a variety of experiences providing urgent and emergency care in various settings.

Q: Turning to U.S. Exhibit 78540 (Samet Reference Exhibit 1), is that a true and accurate copy of your curriculum vita updated to October 21, 2003?

A: Yes.

Q: Your CV says that you were the author and editor of 16 books and monographs, including a book entitled <u>The Epidemiology of Lung Cancer</u> published in 1994; is that correct?

A: That's correct.

Q: What does it mean to author a chapter in a book?

A: A chapter is a contribution to a textbook or a collection of papers on some special subject. It is generally a review of papers on a particular topic. I have written chapters for respiratory textbooks, general medicine textbooks, and others. I have authored approximately 123 chapters for books.

Q: What is a peer-reviewed article?

A: These are articles of original research where data have been gathered, collected, analyzed and written into a paper for publication in what we call the peer-reviewed literature. Publication of a peer-reviewed article means that it was sent to a journal and the peer reviewers decided that the work was acceptable for publication because it provides new knowledge. That's what we mean by "peer review." I have authored about 230 peer-reviewed articles.

Q: How many other professional papers have you authored or edited?

A: Through October 2003, I had authored or edited more than 50 papers for proceedings of meetings; over 125 case reports and editorials; and I have had approximately 100 abstracts accepted for publication.

Q: Let's discuss a few of your peer-reviewed journal articles on smoking and health for the benefit of the Court. You have a peer-review publication entitled, "Respiratory Disease in a New Mexico Population Sample of Hispanic and Non-Hispanic Whites" published in 1982. Would you explain that study to the Court?

A: This is a study that I did shortly after going to New Mexico in 1978 with funding from the University of New Mexico and by the American Lung Association. It was a survey of approximately 1700 residents of Albuquerque, New Mexico, half Hispanic and half not. We gathered information on smoking and the rates of respiratory symptoms that they had experienced, and also the respiratory diseases with which they had been diagnosed.

Q: Turning to an article entitled, "Cigarette Smoking and Lung Cancer in Hispanic Whites and Other Whites in New Mexico" published in 1985. Would you explain that study?

A: This study was funded by the National Cancer Institute. It is a case-control study directed at the causes of lung cancer in the state. In a case-control study of lung cancer, exposures and characteristics of lung cancer cases and similar controls, without cancer, are compared. The intent of the study was to try to understand why we had observed lower rates of lung cancer in Hispanic residents of the state compared with non-Hispanic residents. That study generated more than ten peer-reviewed publications exploring smoking and lung cancer and other causes of lung cancer.

Q: Turning to the next publication entitled, "Respiratory Diseases and Cigarette Smoking in a Hispanic Population in New Mexico" published in 1988. Would you tell the Court about that study?

A: This was another study in the population in New Mexico that was funded by the National Heart, Lung and Blood Institute of the National Institutes of Health. This was a door-to-door survey involving approximately 700 households; over 2,000 persons were asked about smoking and other risk factors for disease. We measured lung function, blood pressure, height, weight and biomarkers of exposure to tobacco smoke. This particular paper provides a description of the findings.

Q: What are biomarkers of exposure?

A: Biomarkers refer to compounds or other indicators that we can measure in a body fluid, a tissue, air breathed out by people, and so forth that demonstrate exposure to a possible source of disease.

Q: What biomarkers of exposure did you measure in that study, doctor?

A: We collected saliva for analysis of cotinine, which is a nicotine metabolite. These analyses were used to assess passive smoking and also nicotine uptake by active smokers.

Q: Turning to the next publication entitled, "Lung Cancer Mortality and Exposure to Radon Progeny in a Cohort of New Mexico Underground Uranium Miners" published in 1991. Would you tell us about that study?

A: When I returned to New Mexico in 1978, the state was the site of the free world's largest uranium mining industry. There was a great deal of concern about the risks of radiation for the miners, so we undertook a large epidemiological study that assessed the risks associated with

radon particularly for lung cancer. A component of that study was to try to understand how smoking and radon act together to cause lung cancer.

Q: What were the conclusions of that study, Doctor Samet?

A: One of the findings of the study, unfortunately for the miners, was that there were substantial risks of lung cancer associated with radon. We also found evidence of synergism in the combined effect of smoking and radon.

Q: Have you been involved with any national scientific committees on the subject of radon?

A: Yes. For the National Research Council, which is essentially the operating arm of the National Academy of Sciences that was commissioned by Congress to provide guidance to the nation on matters of science and policy, I was a member of the committees known as The Biological Effects of Ionizing Radiation or BEIR Committees. I have been a member of several similar committees and chaired the sixth BEIR committee, which covered the topic of radon comprehensively.

Q: Do you currently serve on any committees of the National Research Council?

A: Yes, at present I am chairman of the Board of Environmental Studies and Toxicology. The Board has the responsibility of overseeing studies carried out by the National Research Council that address issues related to the health effects of environmental exposures. This scope is broad, extending from basic science to public policy. The Board of Environmental Studies and Toxicology is the largest such board of the National Research Council.

Q: Have you been involved with committees of the Environmental Protection Agency?

A: Yes, I have frequently served on committees of the Environmental Protection Agency's Science Advisory Board. At present, I am a consulting member of The Clean Air Scientific

Advisory Committee (CASAC) which provides scientific input into the development of the major air quality standards.

Q: Turning to an article entitled, "Sleep/Heart Health Study Design Rationale and Methods" published in 1997. Would you explain that study?

A: Yes. Since early 1995, I have been involved with a multi-center study on sleep and sleep disordered breathing funded by the National Institutes of Health. The medical problem being studied is breathing pauses during sleep and risk for cardiovascular disease, often referred to as sleep apnea. This is a multi-site study involving about 6,000 persons, who are now going to be followed for their risks of heart disease in relationship to the sleep that we measured.

Q: As part of the data that is gathered for this study, are you collecting any information on smoking?

A: Yes.

Q: Are you currently involved with research on tobacco and health?

A: Yes, in a number of projects in the United States and many other countries. There is a range of projects, but all have the goal of producing evidence for tobacco control.

Q: Doctor, have you worked on the reports of the Surgeon General of the United States regarding smoking and health?

A: Yes, as author and editor, including serving as the Senior Scientific Editor for the most recent Surgeon General's report that was released on May 27, 2004. I am also familiar with previous reports as an author, editor and scientist.

Q: What aspect of smoking and health problem did the 1984 Surgeon General's report address?

A: That report addressed chronic obstructive lung disease, which is another name for COPD. I wrote a portion of a chapter for that report on smoking, lung function and development of COPD. This was my first contribution to these reports.

Q: What smoking and health issue did the 1985 Surgeon General's report address?

A: Smoking and occupation. I wrote a chapter on methodological issues related to smoking and lung disease in the workplace and I was also Consulting Scientific Editor.

Q: What smoking and health issue did the 1986 Surgeon General's report address?

A: That report addressed involuntary smoking which is also called passive smoking and secondhand smoking. I was one of the authors of the 1986 report as well as one of the Consulting Scientific Editors for the report.

Q: What smoking and health issue did the 1989 Surgeon General's report address?

A: The 1989 report, the 25th anniversary report, was a review of the information gained over 25 years since the 1964 Surgeon General's report. I contributed to the chapter on health consequences of smoking.

Q: What smoking and health issue did the 1990 Surgeon General's report address?

A: That report was on the health benefits of smoking cessation. I was the Senior Scientific Editor of that report. I also authored and contributed to several of the chapters in that report

Q: Did you also make a contribution to the 1994 Surgeon General's report?

A: Yes, I did. That report was on children, smoking, and the health consequences of smoking by children. I authored the chapter on the health consequences of smoking by children.

Q: What smoking and health issues did the Surgeon General's report of 1998 address?

A: Smoking and health in minority populations. I also contributed to that report, addressing health effects of smoking in minority populations.

Q: You also had a role in the recently released 2004 Surgeon General's report?

A: Yes. I was the Senior Scientific Editor for this report which comprehensively covered the health effects of active smoking. I also was co-author on a number of the chapters. A number of new causal determinations were made for diseases not previously linked to smoking.

Q: Have you also written for any Surgeon General's reports currently in development?

A: Yes, I have.

Q: What do they address?

A: I am the Senior Scientific Editor for the pending 2005 report, which will address passive smoking.

Q: Doctor Samet, have you also served as a reviewer of the Surgeon General's reports?

A: Yes. For a number of years I have reviewed outlines of the reports as they have been developed, selected chapters from the reports, and then the final reports themselves.

Q: Have you been officially recognized for your contributions to Surgeon General's reports?

A: Yes. In 1990, I received the Surgeon General's Medallion for my service. In addition, selection as Senior Editor of the report is a form of recognition as well.

Q: Doctor, do you also review or work as a reviewer of scientific literature?

A: Very frequently.

Q: Can you tell us what a reviewer of scientific literature does?

A: A reviewer is sent manuscripts, people's scientific work, describing their data and the findings from data analysis and their interpretation and discussion of findings. The reviewer assesses whether this work will make a contribution, whether the work has used the state of the science, and whether the authors have properly analyzed and interpreted their data and findings.

Over the years, for many, many journals such as the *Journal of the American Medical Association*, the *New England Journal of Medicine*, *Lancet*, the *British Medical Journal*, and the *Journal of the National Cancer Institute*, *Cancer*, and many journals in the areas of cancer, respiratory diseases, environment, and public health, I have served as a reviewer of scientific work.

Q: How many scientific articles have you reviewed in your career?

A: Probably thousands.

Q: Are you also involved with smoking and health issues in other countries?

A: Yes, I am. At Johns Hopkins, I established and direct the Institute for Global Tobacco Control which carries out this work. For nearly a decade, I have been working with colleagues in the Chinese government through the Chinese Academy of Preventive Medicine, the Chinese Academy of Medical Sciences, and the Chinese Association on Smoking and Health, providing collaboration and assistance with regard to their national study of smoking and surveys related to smoking among Chinese children, trying to understand factors influencing the decision to smoke, and also among urban and rural populations in China, studies of nicotine dosing, and studies of interventions to reduce secondhand smoke exposure.

Q: With regard to the Johns Hopkins School of Public Health's Institute for Global Tobacco Control, you have testified that you are its director, what does that institute do?

A: This is an organization that was established about five years ago to work on the issues of tobacco control around the world. The Institute's staff work with countries in the developing world, such as China, countries in Southeast Asia and elsewhere, doing research and science that will help establish a sound scientific basis for tobacco control policy. We have funding from a number of organizations for this work.

Q: In connection with your work on smoking and health, have you been involved with the World Health Organization's International Agency for Research on Cancer?

A: I was a member of the 1985 working group on smoking that resulted in the 1986 International Agency for Research on Cancer monograph on smoking. I also chaired the 2002 Working Group on Active and Passive Smoking.

Q: Are you involved with the National Cancer Institute?

A: Yes, I have served on the Board of Scientific Counselors of the National Cancer Institute and I have contributed to the National Cancer Institute's Smoking and Tobacco Control monograph series.

Q: What is that monograph series, Doctor Samet?

A: This is a series of volumes published by the National Cancer Institute since 1991 that have addressed specific issues related to smoking and tobacco control.

Q: Were you involved with the first monograph?

A: Yes, the subject of the first monograph was tobacco control titled, Strategies to Control Tobacco Use in the United States: a blueprint for public health action in the 1990's, and I was one of the editors.

Q: To what does the phrase, "the changing cigarette," refer?

A: This phrase refers to the continued modification of the cigarette through various aspects of its design over the years.

Q: Were you also involved with Monograph Seven, The FTC Test Method for determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Report of the NCI Expert Committee, about the Federal Trade Commission test method for assessing tar and nicotine yield of cigarettes?

A: Yes, I authored a chapter for it. I contributed an article on the health consequences of the changing cigarette to Monograph Seven.

Q: When was that monograph published?

A: 1996.

Q: Has the topic of the changing cigarette been revisited by the National Cancer Institute's monograph series?

A: Yes, in 2001, in Monograph Thirteen, Risks associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine.

Q: Were you also a contributor to Monograph Eight of the National Cancer Institute's monograph series, Changes In Cigarette Related Disease Risks and Their Implication for Prevention and Control?

A: Yes, I was one of the editors. Monograph Eight addressed the risks of smoking and mortality over time using data from major U.S. epidemiological studies.

Q: Turning to the professional memberships that are listed in your CV, in what professional societies or organizations do you hold memberships?

A: For many years I have been a member of the American Thoracic Society and the Society for Epidemiological Research. I was president of the Society for Epidemiological Research in 1990. I have also been president of the American College of Epidemiology.

Q: Are you a member of the National Academy of Sciences?

A: Yes. I entered the Institute of Medicine in 1997.

Q: What is the Institute of Medicine or IOM?

A: The IOM comprises the health-related arm of the National Academy of Sciences. There are approximately 500 individuals in the Institute of Medicine who have been selected as leaders

in their field in order to provide guidance to the National Academy on matters of health-related policy in very broad ways and to serve on and support committees.

Q: Doctor Samet, have you also been chair of the Committee on Research Priorities for Airborne Particulate Air Pollution?

A: Yes. This was a six-year committee of the National Research Council that was asked by the Congress to set a research agenda and assign priorities for spending approximately 50 million dollars of research money annually to study air pollution by particles.

Q: Are you on other committees of the National Research Council?

A: Yes, as I mentioned I am currently chair of the Board on Environmental Studies and Toxicology and am a member of the Panel on Science, Law and Technology.

Q: Are you also a member of the Environmental Protection Agency's Science Advisory Board?

A: At the moment I am a consultant member to the Clean Air Scientific Advisory Committee (CASAC) of the EPA. In the past I have been a member of various committees of the Agency's Science Advisory Board.

Q: Are you also an advisor to the American Lung Association?

A: Yes.

Q: Are you the editor of any scientific publications?

A: In the past, I have been Associate Editor of the *American Review of Respiratory Disease*, and Editor of the *American Journal of Epidemiology* and *Epidemiological Reviews*. I am presently Editor of *Epidemiology*.

Q: Are you a member of any editorial boards?

A: Yes, for the *American Journal of Medicine*, the *American Journal of Respiratory and Critical Care Medicine*, *Cancer*, *Epidemiology*, *Biomarkers and Prevention*, and the *European Journal of Epidemiology*.

Q: Doctor, you have been retained as an expert by the United States in this case; is that right?

A: Yes.

Q: What remuneration do you receive from the United States for your engagement as an expert in this case?

A: I do not receive any money personally. Johns Hopkins Bloomberg School of Public Health is compensated at $300 per hour in connection with my work on this case.

Q: Have you been accepted previously to testify as an expert witness?

A: I testified as an expert witness in the State of Minnesota and Blue Cross Blue Shield of Minnesota case in 1998 as an expert in the science of smoking and health. Subsequently, I testified as an expert in the Engle suit in Florida and the Blue Cross Blue Shield of New Jersey case in the United States District Court in Brooklyn in 2001. I also testified in as an expert in two administrative proceedings: before the Federal Trade Commission as an expert against R.J. Reynolds in the Joe Camel proceeding about six years ago and in 1994, on behalf of the Occupational Safety and Health Administration (OSHA) with regard to its proposed rule on indoor air quality.

Q: Have you reviewed the scientific literature on the science of smoking and health?

A: Yes, constantly. As my CV shows, I have been actively studying this topic for many years. In connection with my testimony in Minnesota an extensive database of over 900 studies in the epidemiologic literature was prepared and that database continues to be maintained and

updated by my assistants for many purposes, including for use in my work on the Surgeon's General reports. With the 2004 Surgeon General's Report, the Surgeon General released a database of 1600 articles. As part of my professional activities, I have reviewed many of the reports added to this database as well as other materials.

Q: Have you arrived at any opinions about whether smoking causes disease?

A: Yes.

Q: What conclusions have you drawn?

A: That smoking causes many specific diseases and that smokers are less healthy than nonsmokers generally. Both active smoking and passive smoking (the inhalation of smoke by nonsmokers) cause disease. Smoking also adversely affects reproduction and the developing fetus.

Q: Have you arrived at any opinions about whether lower tar and lower nicotine cigarettes have reduced the health risks of smoking?

A: Yes.

Q: What conclusions have you drawn?

A: That their use has had no clear benefit on the health risks of active smoking.

Q: Have you arrived at any opinions about whether secondhand smoke causes disease and other adverse health effects in non-smokers?

A: Yes.

Q: What opinions have you drawn?

A: That secondhand smoke, which is also referred to as environmental tobacco smoke, causes specific diseases in children and adults as well as other adverse health effects.

Q: Have you prepared a series of exhibits that summarize the facts and data in the scientific and medical literature that form the basis for your opinions in an effort to demonstrate that your opinions are the product of reliable principles and methods and that you have applied those principals and methods reliably to this case?

A: Yes

Q: Doctor, if you would, using U.S. Exhibit 17101 (JS002.1), entitled "Human Bodies – Man and Woman," please explain the human anatomy to the Court briefly, focusing particularly on those organs that are known to be effected by cigarette smoking?

A: Virtually every organ in the human body is affected by smoking. Starting from the top, the Court can see the brain, eyes, nose and the mouth, which leads to the throat, to the larynx where the air passes down into the lung. The nose is, of course, the path for most breathing; some breathing goes on through the mouth depending on the level of exercise. The air passes down the back of the throat, through the larynx or the voice box and into the trachea, which is the tube connecting the larynx to the lung.

We have two lungs, of course, the left and right lung, and sitting between the lungs is the heart, as the Court can see. The heart has its own blood vessels; the heart is a muscle, a pump, and the blood vessels that take the blood into the heart muscle are called the coronary arteries. The blood moves through other arteries to the brain and other organs. The blood leaves the heart through the aorta, which branches to supply blood throughout the body.

Q: Turning to U.S. Exhibit 17102 (JS002.2), entitled, "Abdominal Cavity – Man and Woman with Fetus," can you identify the organs in the abdominal cavity for the court that are affected by smoking?

A: The Court can see a large brown structure, the liver. Next to the liver is the stomach, which connects to the duodenum where it leads into the small intestine. The Court can see the small intestines, a beige mass in the exhibit, and then the larger structure ringing the cavity is the large intestines, the colon and rectum. The Court can also see the bone marrow where blood cells are made. In the separate image of a female, the Court can see the cervix of the uterus and the uterus containing a fetus.

Q: Using U.S. Exhibit 17103 (JS002.3), entitled, "Other Organs in the Abdominal Cavity," can you identify additional organs that are affected by cigarette smoke for the Court?

A: Yes. The Court can see that there are kidneys on both sides, the right and the left kidneys, located on either side of the inferior vena cava and the abdominal aorta. Sitting behind the stomach is the pancreas, a secretory organ that makes digestive enzymes and insulin. The urinary bladder sits low in the abdominal cavity.

Q: Continuing the discussion of anatomy and physiology, would you explain human respiration briefly?

A: During normal respiration, the lungs expand and contract easily and involuntarily. That is, no conscious effort needs to be made for air to enter into or leave the lungs. When air comes in through the nose, it moves to the lung where gases are exchanged, primarily oxygen for carbon dioxide and the carbon dioxide laden air is then expired. The blood leaving the lung is enriched in oxygen and has less carbon dioxide than the blood that entered. The heart then pumps the blood out to the rest of the body through the aorta.

Q: Turning to U.S. Exhibit 17104 (JS004) entitled, "Lung Structure," can you briefly explain that exhibit to the Court?

A: The Court can see that the air travels into the lungs, down the trachea, to the tissue of the lung itself. In the lung, the Court can see the tissue, which has been described as sponge-like. This space corresponds to the air sacs, the alveoli, where gas exchange takes place within the lung. The Court can see the main bronchus coming into the lung, which divides repeatedly. These tubes divide and divide and divide perhaps 16 to 20 times until they reach the level of the bronchioles and alveoli, which are the actual gas-exchanging surfaces of the lung.

On the right-hand side, the Court can also see an alveolus in more detail, and you can see that surrounding the alveolus is a very delicate layer of small blood vessels, capillaries, that bring unoxygenated blood, shown here in blue, to the alveolus, and there oxygenation of the blood takes place.

Q: Turning to U.S. Exhibit 17105 (JS005) entitled, "The Process of Gas Exchange in the Lung," can you explain that exhibit to the Court?

A: In U.S. Exhibit 17105, the Court can see how the blood circulates through this delicate capillary network in the lungs and the exchange of gases, that is, the carbon dioxide passing out and oxygen going into the capillary where the oxygen binds to the hemoglobin within the spherical red blood cells. Then the blood from the capillaries, all these capillaries around the many, many alveoli, join up into larger and larger vessels, returning to the heart to be pumped out through the left side of the heart to the brain and the rest of the body.

Q: Turning to U.S. Exhibit 17106 (JS006) entitled, "Circulatory System," can you describe that exhibit to the Court?

A: Essentially, the heart is a pump. Its right side (the right ventricle) pumps blood that has returned from the body, out to the lungs. That blood is shown in blue. In the lungs, where the blood becomes oxygenated, the blood goes from a bluish color to a pinkish color, as it is

oxygenated, returning to the left side of the heart to be pumped out through the great vessels, like the aorta and carotid arteries, to the brain and the rest of the body.

Q: Let's turn our attention from human anatomy to the tobacco smoke that enters the body when cigarettes are being smoked. What is cigarette smoke made up of?

A: Cigarette smoke is made up of a mixture of particles, which constitute the tars, and gases, such as carbon monoxide.

Q: Looking at U.S. Exhibit 17107 (JS007) entitled, "How Tobacco Smoke Components Enter the Body Through the Lung," doctor, can you explain briefly to the Court how the particles and gases in tobacco smoke enter the body?

A: Cigarette smoke follows the same route as inhaled air. Here, the Court can see the smoke reaching the alveoli, the gas-exchanging surface of the lungs. In the alveoli, the Court can see oxygen and nicotine, represented as yellow triangles, crossing the membranes and entering the bloodstream. Many other smoke components, including toxins and carcinogens, follow this same path, such as the molecules of carbon monoxide, a gas, and particles of tar.

Q: Doctor, what are some of the chemical compounds in cigarette smoke?

A: Scientists have identified thousands of compounds in cigarette smoke. Some of the compounds include: carbon monoxide, nitrogen oxides, cyanide, benzene, radioactive polonium, aldehydes, many toxins, and a number of other human carcinogens.

Q: What is a carcinogen?

A: One straightforward definition is that a carcinogen is an agent that causes cancer. There are agencies, such as the Environmental Protection Agency in the United States and in Europe the World Health Organization's International Agency for Research on Cancer, often referred to

as IARC, that review scientific evidence using specific criteria to designate compounds as carcinogens.

Q: Turning to U.S. Exhibit 17108 (JS008), entitled "Known Carcinogens in Cigarette Smoke," can you explain to the Court what this exhibit shows?

A: This exhibit lists 62 human and animal carcinogens that have been identified in cigarette smoke to date. This data is from a monograph that was published by IARC in 2004, based on the 2002 Monograph meeting that I chaired. This chart represents the conclusions of a multitude of animal and human studies that have been reviewed in numerous IARC publications between 1972 and 2000. These have all met the criteria of this agency for being carcinogens, through a rigorous review process.

Q: Turning back to U.S. Exhibit 17107 (JS007), can you explain to the Court how the components of smoke are transferred to the bloodstream?

A: The lung has the very delicate structure of the alveoli with a large surface area for exchanging gases. The alveoli are the air spaces in the sponge-like structure that we have already discussed. Within the lung, the tubes repeatedly branch to reach very large numbers and they bring the air containing smoke out to these delicate alveoli. The alveolus is surrounded by a network of blood vessels.

When cigarette smoke is inhaled, gases and particulate materials enter the body through the lung, particularly the alveoli. For example, carbon monoxide, a gas, is exchanged across the alveoli. Nicotine is bound to small particles generated by the burning of the cigarette. These particles are deposited in the airways of the lung and the alveoli. The nicotine leaves the particles and diffuses into the blood in the capillaries. Carbon monoxide moves as gas molecules from the alveoli to the capillaries. Carbon monoxide is bound quite tightly by the hemoglobin, in

fact far more tightly than oxygen itself. As the blood returns to the left side of the heart to be pumped out to the brain and the rest of the body, it contains these agents that it picked up during its contact with the smoke in the lungs.

Q: Doctor Samet, you defined epidemiology earlier. Would you give the Court some more detail about the science of epidemiology?

A: Epidemiology is the science of conducting studies of health and disease in the population, describing how much disease there is, and identifying the causes of disease. It also covers interventions to improve health. For example, epidemiologists address cigarette smoking and other factors that may cause disease, carry out scientific studies involving groups of people to understand what factors influence their health.

Q: What are the ways of measuring disease occurrence?

A: Epidemiologists use a number of different kinds of data to describe how much disease there is and also different study designs to understand what the causes of disease are. There are several fundamental measures of disease occurrence. For instance, the mortality related to a disease may be described by its death rate and the occurrence of disease may be described by the incidence rate, denoting the increase in new cases of disease. We also use the prevalence rate, describing the amount of a disease (i.e., the proportion having a disease) in a particular population at a particular point in time.

Q: Turning your attention to U.S. Exhibit 17111 (JS010) entitled, "Development of Lung Cancer in a Population Over Time," can you please explain this diagram to the Court?

A: This theoretical diagram shows a specific example where there are 100 smokers who do not have lung cancer at the start, 20 of them develop it, and subsequently 19 of the 20 smokers

with lung cancer go on to die from that disease. The smokers' experience is contrasted with the experience of never smokers where out of one hundred never smokers starting in the study, only one person develops lung cancer and dies. We have measures for describing how rapidly a disease is developing and causing death. Incidence is the number of new cases of disease, that is, how many people go from not having disease to developing the disease. The rate at which new cases develop is used to describe how fast the disease is developing in the population.

The mortality rate is used to describe the rate at which people die from a disease. For example, for lung cancer, we might calculate the rate at which people die in the population from lung cancer.

The prevalence or prevalence rate is simply the percent of people who have a disease in the population at a particular point in time. For example, COPD is a relatively common disease; right now perhaps 4 percent of adults in the United States above a certain age, say 40 or 50, have COPD. That would be the prevalence, the amount of disease at a particular moment in time in the population.

Q: Doctor Samet, are all three rates, incidence, mortality and prevalence, used in epidemiological research and public health generally?

A: Yes, they are.

Q: Epidemiologists use a concept called "relative risk." Can you explain that concept?

A: Relative risk is a commonly used term that refers to the rate of disease in people who have some particular exposure relative to that of a group of people who do not have that exposure. For example, we can compare the relative risk for lung cancer comparing current smokers to never smokers in U.S. Exhibit 17111 (JS010). How is relative risk calculated? In that exhibit, we have 100 people who smoke and 100 people who don't smoke. Over time 20 of

the smokers develop lung cancer but only one of the never smokers develops lung cancer. We could describe the relative risk for developing lung cancer from being a smoker as 20 to one (20/100 ÷ 1/100).

The relative risk is a term commonly used in describing the association between a factor that causes a disease, say smoking, in comparison to those not exposed to that factor.

Q: Is there a value of relative risk that epidemiological studies have shown for smoking and lung cancer today?

A: Many studies have addressed the relative risk of lung cancer in smokers. Those estimates now center around an increased relative risk of 20 to 1 or more for people who currently smoke compared to never smokers.

Q: Doctor Samet, as shown in U.S. Exhibit 17111 theoretically, if you had 100 smokers and 100 never smokers, over time, 20 of the smokers would develop lung cancer, and only one of the nonsmokers would. Is that the implication of a relative risk of 20?

A: Yes. Moving to the large general population, these scientific measurements of relative risk indicate that the rate at which smokers develop lung cancer is 20 times higher than the rate at which never smokers develop lung cancer. The relative risk has been estimated to be even higher for those smoking the greatest amounts.

Q: This relative risk of 20 times for lung cancer, how does that compare with other associations between various causes and diseases?

A: A relative risk of 20 is a very strong, or very high risk. Of course, we know about the relative risks of many different factors for many diseases. For example, high blood pressure (hypertension) is associated with increased risk for heart attack, at approximately two to one. This figure of 20 to one for lung cancer is a very high relative risk.

Q: What is "attributable risk?"

A: A second type of measurement that epidemiologists sometimes use is the attributable risk. In this example, to calculate the attributable risk, rather than dividing as we did to calculate the relative risk, we would subtract.

To calculate the attributable risk, we take the risk in the smokers, twenty over 100, and subtract from that the risk in the never smokers, the one over 100, leaving nineteen per hundred. What we are left with is just the extra risk that the smokers have because they were smokers rather than never smokers.

The attributable risk just comes from subtracting the risk of the never smokers from that of the smokers.

Q: Can you briefly describe for the Court the different types of epidemiological studies that are conducted?

A: Yes. There are two broad classes of studies: experimental and observational. In experimental studies, the exposure to a suspected disease causing or disease alleviating agent is assigned by the investigator. Such studies are often done to determine if medication works for treating or reducing risk of disease. They involve randomly assigning people to the treatment group where the drug or active agent is provided or to the control group for whom a different drug, placebo or activity is prescribed. These are often called randomized clinical trials. Of course, such experiments cannot be done with smoking which causes disease. It would not be ethical to assign people randomly to smoke or not to smoke. With regard to experimental research into smoking, scientists have done some experimental studies to look at the benefits of cessation because that is ethical, taking away something that causes increased risk of disease.

In examining the risks of smoking, researchers have relied on observational studies, that is, going to the population and taking advantage of the "natural experiment" of some people smoking and some people not.

Researchers use the study designs that I have listed and defined in U.S. Exhibit 17112 (JS011.1) to describe the risks of disease in smokers as compared to nonsmokers. The technical names for these observational studies are cohort studies, case-control studies, and cross-sectional studies or surveys.

Q: Doctor, using U.S. Exhibit 17113 (JS011.2), can you describe a cohort study?

A: Yes, consider enrolling a group of smokers and a control group of never smokers today and then following them forward over time and periodically looking at each person in the two groups to see if they develop diseases like lung cancer or COPD. This would be an example of a cohort study; we begin with exposed and not exposed persons for comparison and follow for the development of disease.

If an investigation began today and followed these two groups over time to see if they develop lung cancer and compare the rate of disease in smokers to never smokers, then this research would be a cohort study.

The Court may already be familiar with some famous cohort studies, the Framingham Study of Heart Disease, or perhaps the two American Cancer Society cohort studies, that are often referred to as Cancer Prevention Studies I and II (CPS I AND CPS II). Those studies involved enrolling very large groups of smokers and never smokers, about one million each, and then doing exactly what I have described, that is, following them over time and recording the development of any disease. Sometimes scientists also call this design a prospective study because the disease of interest develops in the future.

Q: Using U.S. Exhibit 17114 (JS011.3), can you please describe the research design of a case-control study?

A: Another way to study whether smoking or other factors cause disease is to start with people who already have the disease of interest, like lung cancer, and a control group of people who are similar in important respects except that they do not have the disease. In this design, which is called a case-control study, researchers look backward in time and ask whether any of these individuals in the study smoked and, if so, how much did they smoke. In other words, the study evaluates whether there are important differences between those people who have lung cancer and those in the control group who do not have lung cancer. In this example, having determined the smoking behavior of the two groups, we might compare the rate of smoking in those who have lung cancer and the rate of smoking among those who do not. By doing that in a case-control study, it is possible not only to calculate a measure of the relative risk for developing the disease of interest between smokers and never smokers but also to examine the dose-response relationship between amount or duration of smoking and disease risk.

Thus, cohort studies start with smokers and nonsmokers without disease, follow them over time and observe any incidence of disease. The case-control study starts with people with disease, people without disease and looks back to see who was exposed and how much. These two observational research designs are sometimes thought of as prospective (cohort) and retrospective (case-control).

Q: Using U.S. Exhibit 17115 (JS011.4), can you please describe the research design of a cross-sectional study?

A: The last observational research design is the survey or cross-sectional study. In a survey, we observe a group at just one particular moment in time. In a study of smoking, participants

would be evaluated to see who has the disease of interest among smokers and never smokers. For example, a researcher might go to a community, go door to door, and measure lung function to see who has COPD and ask questions about current smoking. Subsequently, the prevalence of COPD would be compared between smokers and never smokers. This research design is called a survey or cross-sectional study and differs from the other two designs by looking at exposure and disease at one particular point in time only.

Thus, the three main designs for studying smoking as a cause of disease are: the cohort study starting with smokers and never smokers without disease and following them over time; the case-control study starting with people with disease and without disease and looking back to determine their smoking; and, the cross-sectional study or survey, looking at just one particular moment and recording information about the disease of interest, smoking, and other relevant factors or personal characteristics.

Q: In general with regard to cohort studies, for how long a period of time do you talk about as far as following these people into the future?

A: A scientist may learn something very quickly from a cohort study if a disease is common and develops quickly, but further follow-up is often helpful. One famous cohort, for example, the British Physicians Study, was started in 1951, and has now completed 50 years of follow-up. The American Cancer Society's second study, CPS-II, which started in the early 1980's, is still ongoing. These studies continue to supply important information as the researchers keep receiving new information from follow-up.

Q: Doctor Samet, can bias affect the results of epidemiological studies?

A: Yes, it can.

Q: How?

A: By "bias," we are referring to any distortion of the findings of an epidemiologic study away from the truth. In epidemiologic research, there are three different kinds of bias: information bias, selection bias, and a problem we call confounding. Each of these may interfere with the correct interpretation of research data, but scientists have developed techniques for examining potential bias, identifying valid concerns about their consequences, and reducing or eliminating bias where necessary.

Q: Would you give the Court an example of information bias?

A: Information bias means that the information obtained in the study may have some error. This error leads to incorrect classification on exposure or outcome, referred to as misclassification. For example, in a study if someone who smokes, instead of correctly reporting that they are a smoker, or the correct amount of their smoking, gives incorrect information that would be an example of information bias.

Q: Would you give the Court an example of selection bias?

A: Selection bias refers to bias coming from the way that people are selected to be in the study. For example, someone might be doing a survey and perhaps people who smoke and are also sick are less likely to participate in the study than those who are healthy. Such bias would occur through the selection of subjects to be in the study and may introduce some distortion in the findings.

Q: Would you give the Court an example of confounding, the third type of bias?

A: Confounding refers to the bias that arises when the effect of one factor is mixed up with the effect of the factor that we want to study.

For example, let's say a researcher is investigating the risk of heart attack associated with high blood pressure, and those who have high blood pressure are also more likely to have high

blood cholesterol levels, another cause of heart attack. When the researcher assesses the effect of hypertension, the apparent effect of hypertension could be mixed up with that of having a cholesterol level that was high. The resulting assessment of the effects of high blood pressure, we would say, might be confounded by the effects of having high blood cholesterol.

Q: Doctor, how do epidemiologists correct or deal with bias?

A: Researchers are always concerned about bias. We know that bias can affect observational studies. As studies are designed, we think about how the information will be collected and ultimately analyzed, we look at each step along the way for how we can control the effects of bias, or in the end as we analyze the data and interpret it, try to find out if bias occurred and what its effects may have been.

Q: How do epidemiologists correct for confounding?

A: There is often concern about confounding, that is, the effect of one factor being mixed up with that of the factor under study. One basic approach used to address confounding is stratification. Using stratification, we divide the subjects of the study up into different groups of people who are alike on the factors that might be confounders. For example, when studying hypertension, we would look at the effects of having high blood pressure in people with low cholesterol and high cholesterol separately. This way we are always putting the data of the group, the information from people, into piles of like and like, and trying to understand the effects within each group. We also use statistical approaches for this same purpose.

Q: So in comparing like to like, Doctor Samet, are researchers attempting to measure the differences between these two groups?

A: What we would want to do in the end is to have the data lined up into piles of like and like, differing only in the effects of the factor that we are interested in studying. Since we are

examining smoking, we would try and put the data into these piles for any confounding factors, comparing smokers and non-smokers in groups that are alike.

Q: In that way can you isolate the effect of smoking?

A: Yes. This would be one strategy that would allow us to isolate the independent effect of smoking from the effects of any potential confounding factors. We can also accomplish this same sorting by using statistical methods, called multivariate models.

Q: What is a multivariate model?

A: It is a statistical tool for examining the effects of several variables simultaneously.

Q: Doctor, let's turn now to some selected epidemiological studies concerning smoking and health so that we can talk about these research design concepts in a concrete way. The first study is a case control study by Wynder and Graham, U.S. Trial Exhibit 63445 (JS012). Can you describe that study?

A: This is a paper published in the *Journal of the American Medical Association*, May 27th, 1950, entitled "TOBACCO SMOKING AS A POSSIBLE ETIOLOGIC FACTOR IN BRONCHIOGENIC CARCINOMA" by Ernest L. Wynder and Evarts A. Graham. This is a case-control study. It is the type that compares the exposures of people who have a disease, in this instance, lung cancer, with that of controls who are similar to the cases, but do not have lung cancer. This was a case-control study examining patients in the United States: 605 patients who had lung cancer, and 780 controls without lung cancer. By interview, they provided information about their smoking.

Q: Did you review this study as part of your investigation in this case?

A: Yes.

Q: Does this study form part of the basis of your opinions in this case?

A: Yes, it does.

Q: Do you consider this article to be a reliable authority in the published scientific literature?

A: I do.

Q: Turning now to U.S. Exhibit 17116 (JS013) entitled, "Wynder & Graham Case-Control Study (1950), Relative Risk of Lung Cancer, Current Smokers versus Never Smokers" does this exhibit summarize the results of that study?

A: Yes. This exhibit shows the results of this study, expressed as relative risk values; for never smokers, who smoked zero cigarettes a day, the relative risk is set at one as a reference value. The relative risks are then shown by levels of increasing numbers of cigarettes smoked per day up to 35 or more a day. The original report did not include these values, so I noted that I made the calculation from the data in the paper.

There are two important aspects of this study. First, the Court should see that, in general, as the number of cigarettes smoked per day goes up, the relative risk rises from 2.2 for those who smoke one to nine cigarettes per day to nearly 30 for those who smoke more than a pack a day. This is referred to as a dose-response relationship or an exposure-response relationship. Second, the Court should also note just how high the relative risk values rise. At the higher levels of smoking, smokers have about 30 times the risk of lung cancer compared to the never smokers. There are very few risk factors for disease that have such a strong effect.

Q: Turning your attention to U.S. Exhibit 62855 (JS014), can you identify that exhibit, doctor?

A: This is a publication in the *British Medical Journal* in 1950, Volume II, pages 735 through 748 entitled "SMOKING AND CARCINOMA OF THE LUNG, PRELIMINARY

REPORT" by Richard Doll and A. Bradford Hill. This is a study similar in design to the Wynder and Graham study. It is a case-control study involving 709 persons coming to a hospital in London with a presumptive diagnosis of lung cancer and a group of controls not having lung cancer. These two groups were interviewed concerning smoking and other factors.

Q: Have you reviewed that study as part of your investigation in this matter?

A: Yes.

Q: Does that study form a part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider the article a reliable authority in the published scientific literature?

A: Yes.

Q: Directing your attention to U.S. Exhibit 17117 (JS015), which is titled "Doll & Hill Case-Control Study (1950), Relative Risk of Lung Cancer, Current Smokers versus Never Smokers: Men," would you please explain what that exhibit summarizes to the Court?

A: Yes. This exhibit summarizes, as in the previous study, the relative risk for lung cancer in men, comparing current smokers to never smokers by the number of cigarettes smoked per day. As in the other study, we see a dose-response relationship, the relative risk rises with the number of cigarettes smoked per day, again reaching values at the higher levels of smoking around 30 for those smoking more than a pack a day. These figures are not in the tables that accompany the article, rather this exhibit summarizes not just the data in the article but also a recalculation and redisplay of some of that data.

Q: Doctor Samet, looking at the results in U.S. Exhibit 17117 (JS015), the Court can see that the intensity of cigarette smoking is shown; for example, one to four, five to 14, 15 to

24, 25 to 49, and 50. Now is that the number of cigarettes smoked per day by smokers in the study?

A: Yes. That legend refers to broad groupings of the numbers of cigarettes smoked per day by the smokers who participated in the study. For example, 15 to 24 include only those smokers who reported smoking in the range of 15 to 24 cigarettes per day.

Q: How many cigarettes are in a pack?

A: Typically twenty cigarettes are in a pack in the United States.

Q: Doctor, let's turn from case-control studies to cohort studies. Directing your attention to U.S. Exhibit 86855 (JS016), would you identify that study for the Court?

A: This is a paper from the *British Medical Journal*, June 22, 2004, entitled "Mortality in relation to smoking: 50 years' observations on male British doctors" by Richard Doll and his colleagues. This was a study started in 1951 by Sir Richard Doll and Sir Austin Bradford Hill following their earlier case-control study. Approximately 34,000 male physicians and another group of about 6,000 female physicians were enrolled in this cohort study. The researchers periodically gave their findings as follow-up continued up through 50 years. The 20-year data were reported in 1976; the 40-year data were reported in 1994; and the 50-year results were published in June, 2004.

Q: Doctor, did you review this study, U.S. Exhibit 86855 (Samet Reference Exhibit 16), as part of your investigation in this case?

A: Yes.

Q: Does this paper form part of the basis of your opinions in this case?

A: Yes, it does.

Q: Do you consider this article to be a reliable authority in the published scientific literature?

A: Yes.

Q: Directing your attention to U.S. Exhibit 17118 (JS017) entitled, "British Doctors Study," would you describe for the Court the study design of the British Doctors Study.

A: This was a prospective cohort study now involving 50 years of follow-up. At the time that the study was started, it was one of the first cohort studies initiated on smoking and health, Doll and Hill did something practical. They were able to identify all the physicians who were registered in the United Kingdom. They thought that physicians would be interested in participating in the study, and would know how to fill out a questionnaire, and that they would be able to remain in contact with them, because even when they change addresses, they remain registered as professionals.

Doll and Hill also selected a very large professional group whom they thought would also have a mix of current smokers, former smokers and never smokers. At that time in the United Kingdom, physicians smoked just as much as the population in general. The rate of smoking in the cohort was probably around 50 percent or more when the study started.

Some of the diseases that were looked at in terms of mortality rates included lung cancers, chronic obstructive pulmonary disease, coronary heart disease, that is, diseases of the heart vessels associated with heart attack, and other diseases.

In this study, they periodically asked the doctors about the status of their smoking behavior, so that they found out whether non-smoking doctors had started and whether smoking doctors had stopped.

Q: Directing your attention to U.S. Exhibit 17119 (JS018) entitled, "Relative Risk of Lung Cancer Death at Various Points of Follow-up in the British Doctors Study, 1951-2001: Men," would you explain to us what is summarized in that exhibit?

A: This table describes the results of the British doctors study as it unfolded over time, first at ten years of follow-up, then at 20 years of follow-up, and going on down the table, at 50 years of follow-up. At each point of follow-up, the relative risk of developing lung cancer is shown for the reference group never smokers, zero cigarettes a day, and then the various smoking groups, one to 14 cigarettes a day, 15 to 24, and 25 or more a day. The overall increase in relative risk of dying of lung cancer for current smokers compared to never smokers is shown at the top of each column.

At each time point there is a very strong increase in risk for current smokers for lung cancer compared with never smokers, and at each point in time we can see a very strong dose-response; that is, an increase in relative risk for lung cancer going from one in the never smokers by definition to 20 or more in each of the various time periods for smokers who smoked more than a pack a day.

Q: At the 50-year follow-up, would you explain to the Court the various legends that indicate cigarettes per day and relative risk of mortality?

A: Certainly. At the 50-year follow-up for current smokers, the overall risk, relative risk compared to never smokers was 14.65, or approximately 15. Going through the row representing the dose-response: never smokers are one by definition, persons smoking one to 14 cigarettes a day 7.7 relative risk, 15 to 24 cigarettes a day 13.7 relative risk, 25 or more cigarettes a day, a relative risk of 24.5.

Q: This rise in relative risk across greater intensities of smoking is referred to as a dose-response?

A: Yes, dose-response. The presence of dose-response, is strong evidence for causality, in part because it is difficult to explain dose-response by the uncontrolled effect of another factor.

Q: Directing your attention to U.S. Exhibit 17121 (JS019), would you explain that exhibit to the Court?

A: Certainly. This exhibit is entitled "Relative Risk of Coronary Heart Disease Death in the British Doctors Study at Various Points of Follow-up, 1951-2001: Men."

It is laid out like the last exhibit. The Court is looking at the findings of the British Doctors study, at 10 years, 20 years, 40 years, and 50 years of follow-up. The information is shown for current smokers compared to never smokers, and then the dose-response findings by number of cigarettes smoked. One thing that the Court may have already noticed is that in this study, for coronary heart disease, the relative risks are lower than what we saw for lung cancer; instead of relative risks of 20 or 25 or 30, the values range from 1.3 to about two.

At 20 years, the relative risk for Coronary Heart Disease, sometimes called CHD, is 1.9 for those who smoked 25 or more cigarettes per day. Lower relative risks are found for coronary heart disease because it has several other causes besides smoking. Consequently, the study measured the added effect of smoking on top of the effects of these other factors. Yet, we still see evidence of dose-response with the relative risks tending to rise as the exposure to cigarette smoke increases. So, across the 50 years of follow-up, the Court can see that the dose-response relationship persists.

Q: Please direct your attention to U.S. Exhibit 17123 (JS020) entitled, "Relative Risk of COPD Death in the British Doctors Study at Various Points of Follow-up, 1951-2001: Men," would you explain to the court what COPD stands for?

A: Yes. COPD stands for chronic obstructive pulmonary disease. COPD is the name presently used for a disease that often in the past has been called "emphysema" or sometimes "chronic bronchitis." COPD refers to the irreversible damage of the lung that results in shortness of breath and functional limitation in current or former smokers. The lungs of people who have COPD show emphysema and other signs of damage.

Q: Doctor Samet, would you go to the 50 years' follow-up and explain the results to the Court?

A: Yes. This table is laid out very much like the other summary exhibits. The overall increase in risk for current smokers compared to never smokers is a relative risk of 14.18. The dose-response, one for the never smokers, rises up to 23.7 increased risk for COPD deaths for those smoking 25 or more cigarettes a day.

The Court can see that in contrast to the heart disease data, and more like the lung cancer, the relative risks are very high, the dose-response relationship is very steep, and the risk pattern reflects the fact that at this point in developed societies, the United Kingdom, the United States, there are very few causes of COPD other than tobacco smoking.

Q: You have explained the results for men in the British doctors cohort study to the Court, but that study also tracked a large number of women doctors as well. Please direct your attention to U.S. Exhibit 17125 (JS021), which is entitled "Relative Risk of Lung Cancer Death in the British Doctors Study at 22 Year Follow-up, 1951-1973: Women," would you explain to the Court the figures that we see in that exhibit?

A: These are findings for the relative risk of lung cancer. I should make clear that this is death from lung cancer in the women, approximately 6,000, included in the British doctors study at 22 years of follow-up, showing the dose-response relationship information. The range of the relative risk of dying from lung cancer varies from 1.3 for women doctors who smoked 14 cigarettes or less to nearly 30 for those who smoked more than a pack a day, very similar to the men in the study.

Q: Doctor, I want to direct your attention now to U. S. Exhibit 17126 (JS022), a summary exhibit entitled "Relative Risk of Coronary Heart Disease Death at 22 year Follow-up in the British Doctors Study, 1951 to 1973:Women," would you describe for the Court the data on that chart.

A: Yes. This is information on relative risk for death from coronary heart disease in women participants in the British doctors study at 22 years of follow-up, corresponding to 1973.

Q: What does this exhibit show?

A: The Court can see that there is an approximate doubling of relative risk of coronary heart disease death, looking at women smoking 15 or more cigarettes per day.

Q: Doctor Samet, please turn now to another cohort study, the Framingham study, U.S. Exhibit 64190 (JS023). Would you identify that study?

A: This is a paper published in the *Journal of the American Medical Association*, February 19, 1988, entitled "Cigarette Smoking as a Risk Factor for Stroke, The Framingham Study" by Philip Wolf, Ralph D'Agostino, William Kannel, Ruth Bonita and Albert Belanger. Framingham refers to Framingham, Massachusetts, which is where the study was done. Framingham is a small town just to the west of Boston. The study originated in the late 1940's because it had become clear by then that mortality from coronary heart disease was rising in the U.S., but no

one quite understood why. This study was undertaken as a prospective cohort study in this community to identify the causes of coronary heart disease. It involved a population of over 5,000 men and women. The participants in the study had a fairly extensive set of examinations every two years. The principal measures of outcome, of interest were coronary heart disease and stroke, among others. This population was followed to identify incidence; that is, new occurrences of disease, and also death and the specific causes of the death of the participants in the study.

Q: Doctor, have you reviewed this paper as part of your investigation in this case?

A: Yes.

Q: Does the article form part of the basis of your opinions in this case?

A: Yes.

Q: Doctor, do you consider this article to be a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor Samet, please turn your attention to U.S. Exhibit 17128 (JS024.2), entitled, "Framingham Study – Relative Risk for Stroke Incidence," would you explain how this exhibit summarizes the results of the study for stroke.

A: This exhibit summarizes the results in the Framingham study for the incidence or occurrence of stroke separately for women and men. The Court can see the relative risks for stroke, which have been adjusted for age and also for one factor that is also a cause of stroke, that is, hypertension. The Court can see the dose-response in relative risk by numbers of cigarettes smoked per day, and that in women and in men, there is approximately a similar dose-response relationship between the number of cigarettes smoked and the relative risk for stroke.

The relative risks for stroke vary from about two for those smoking two packs of cigarettes per day down to 1.4 for those smoking a pack a day.

Q: The relative risks summarized in U.S. Exhibit 17128 (JS024.2) for stroke are not as high as for lung cancer and COPD. Why?

A: These values for stroke are similar to the relative risks that we saw in the British doctors study for coronary heart disease. Stroke, like heart disease, has a number of causes and it has many of the same underlying mechanisms as CHD. So that here the Court is seeing the additional risk from smoking as it operates on the background of risk posed by these other causes.

Q: Doctor, I now want to refer you to another cohort study, the American Cancer Society's Cancer Prevention Study, U.S. Exhibit 88626 (JS025), would you identify that?

A: Yes. This is a paper published in the *American Journal of Public Health*, September of 1995, entitled "Excess Mortality among Cigarette Smokers: Changes in a 20-Year Interval" by Michael Thun, Cathy Day-Lally, Eugenia Calle, Dana Flanders and Clark Heath. This paper describes the design of two studies done by the American Cancer Society, both involved one million Americans, and both were studies done by the volunteers of the American Cancer Society who assisted in the recruitment of the participants to these studies and collected the data. The first study, sometimes referred to as CPS I, went on from 1959 to 1972. CPS II, which is still in progress, began in 1982 and also involves about a million Americans, not the same people who are in CPS I, but a new group who were enrolled into CPS II. These two groups were followed and the American Cancer Society identified each person who has died and gains information about the cause of death. In CPS I, the participants were periodically contacted to reassess their smoking.

Q: Have you reviewed that publication as part of your investigation in this case?

A: Yes.

Q: Does that article form part of the basis of your opinions in this case?

A: Yes.

Q: Do you consider that article to be a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor, please turn your attention to U.S. Exhibit 17129 (JS026) summarizing the American Cancer Society's Cancer Prevention Studies. The title of the summary is "Cancer Prevention Study I and II: Relative Risk, Current Smoker vs. Never Smoker." Would you explain that exhibit to the Court?

A: The Court can see the values given in two sets of rows for men and women, and then within each group, CPS I and CPS II. The relative risks for death, comparing current smokers to never smokers, are given for a number of causes of death: lung cancer, other cancers linked to smoking, coronary heart disease (CHD), COPD, and stroke.

Consider, for example, lung cancer. For men, the overall relative risk in CPS I, that was 1959 to 1965, looking at the early years of the study, was 11.9 and 1982 to 1986 in CPS II it was 23. In women in CPS I, the relative risk was 2.7, about three, and in CPS II, 12.8.

As we go down the chart for each disease category, the Court can see that all the relative risk values are above one. The Court can also see that in every instance, the relative risk values have risen comparing CPS II to CPS I, approximately 20 years earlier. This rise has been particularly strong in women. For example, COPD, 6.7 CPS I, 12.8 CPS II; lung cancer, 2.7 CPS I, '59 to '65, 12.8 in the 1980's. The Court can also see the strength of the relative risk from

cigarette smoking in causing these diseases, going from lung cancer, 23-fold increase, to coronary heart disease, a doubling of the risk of dying for the current smokers compared to never smokers.

Q: Doctor Samet, you said "never smokers." What do you mean by "never smokers?"

A: In this study, the term “never smokers” refers to individuals who reported themselves as never smoking a significant number of cigarettes.

Q: Directing your attention to U.S. Exhibit 64215 (JS027), would you identify that study for the Court?

A: Yes. This is a paper published in the *New England Journal of Medicine*, 1987, pages 1303 to 9 in Volume 317, entitled “RELATIVE AND ABSOLUTE EXCESS RISKS OF CORONARY HEART DISEASE AMONG WOMEN WHO SMOKE CIGARETTES,” the authors are Walter Willett, Adele Green, Meir Stampfer, Frank Speizer, Graham Colditz, Bernard Rosner, Richard Monson, William Stason and Charles Hennekens. This is another prospective cohort study. It required follow-up of a large group of nurses, approximately 120,000, contributing data to this particular report. This is a study that produces papers very frequently in the medical literature, and there is also a second nurses cohort study in progress, addressing a younger group.

Q: What do you mean by “cohort?”

A: In this cohort study, the population studied is 120,000 nurses who were on rosters of licensed nurses, members of The Nurses Association, and who were asked to participate in this study. They were ages 30 to 55 at the time they were enrolled in the study. Their health was followed in subsequent surveys, including the occurrence of coronary heart disease or heart attacks, cancer, and other health problems. This tracking over time is central to cohort studies.

They answered a questionnaire when they entered the study and then approximately every two years, the nurses answered a follow-up questionnaire. One of the questionnaire items was smoking. The team obtained information from medical records as well. Thus, if a nurse reports that she has had a heart attack on the questionnaire, then medical records are obtained and reviewed. The study tracks the occurrence of new heart attack incidence, and also death, overall and from particular diseases.

Q: You mentioned Frank Speizer. Is that the Dr. Speizer who was your mentor at the Harvard School of Public Health?

A: Yes. This is a paper based on the Nurses' Health Study that I mentioned previously.

Q: Did you review this study as part of your investigation in this case?

A: Yes.

Q: Does the study form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is this study a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor, directing your attention to U.S. Exhibit 17131 (JS028) entitled, "Nurses' Health Study," would you tell the Court how that exhibit summarizes the results of that study?

A: This exhibit provides the combined data for heart attacks that were fatal coronary heart disease, and also for non-fatal heart attacks or the technical term is myocardial infarction. The Court can see the relative risks for current smokers compared to never smokers. The never smokers smoke zero cigarettes per day, by definition while for the current smokers the number of cigarettes smoked per day is: one to 14; 15 to 24; and 25 or more. In this table, the Court can see

something called the "age-adjusted" relative risk estimate. This means that age has been taken into account so that it is as though the ages were similar in each of these groups defined by level of smoking.

Q: When you say that age is taken into account, can you give us an example of what you mean?

A: Yes. In other words, it is possible that people in one of the smoking groups might be older or younger than the never smokers. This potential imbalance in the age in the different groups has to be taken into account by an adjustment so that when we look at the effects of smoking, the age differences between the groups do not distort the results.

Q: Would you explain the row, entitled "Fully Adjusted."

A: Yes. We have two rows of relative risks. One row is age-adjusted only and the other row is the fully adjusted risk estimates with this star. The Court can see that in the age-adjusted row, there is a dose-response with a relative risk rising from one for never smokers to six for those smoking 25 cigarettes or more.

The relative risks in the second row are also adjusted, but the researchers have taken account of potential confounding factors, that is, those factors that might have been mingled with smoking, so that they can look at the effects of smoking independent of the effects of these other factors. The factors that they have controlled for are listed: age, the interval of time of follow-up; Quetelet's index (BMI), a measure of the body mass, that is, the relative weight of the individuals; menopausal status, which influences heart disease risk; family medical history; personal history of diabetes, another risk factor for heart attack; hypertension; and, high blood cholesterol.

The important point is that after controlling for all of these potential confounding factors, the relative risk values, comparing the row where only age has been taken into account with the row where the researchers have taken into account age and these other factors are nearly the same. In other words, while we are often concerned about the potential effects of confounding, in this instance this adjustment for confounders had no impact on the relative risk of smoking.

Q: You have explained to the Court a few studies on smoking and disease, have you reviewed other studies on smoking and disease in order to form your opinions in this case?

A: Yes, I have.

Q: Approximately how many?

A: Thousands.

Q: Did you rely on them in part to form your opinions?

A: Yes.

Q: Are these studies reliable authorities in the published scientific literature?

A: Yes.

Q: Doctor, did you also review reports of the Surgeon General of the United States on smoking and disease as part of your investigation in this case?

A: Yes, I did.

Q: What public reporting function does the Surgeon General perform by issuing these reports?

A: Previously, a report was required annually by law. Now the reports are still released to assure that the evidence on smoking and health is periodically assembled and reviewed.

Q: Turning to U.S. Trial Exhibit 64057 (no JS number) entitled, Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, did you review this 1964 report?

A: Yes.

Q: Is that the report regarding lung cancer?

A: And other diseases, yes.

Q: Do the conclusions in that report form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is that report a reliable authority in the published scientific literature?

A: Yes.

Q: Turning to U.S. Trial Exhibit 63621 (no JS number) entitled, Reducing the Health Consequences of Smoking, did you review this 1989 report as part of your investigation in this case?

A: Yes, I did. The 1989 report was the 25-year progress and summary report.

Q: Do the conclusions in that report form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is that report a reliable authority in the published scientific literature?

A: Yes.

Q: Turning to U.S. Trial Exhibit 64055 (no JS number) entitled, The Health Benefits of Smoking Cessation, did you review this 1990 report as part of your investigation in this case?

A: Yes, I did. That is the Surgeon General's report on the health benefits of smoking cessation.

Q: Who was the senior scientific editor for that report?

A: I was.

Q: Do the conclusions in that report form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is that report a reliable authority in the published scientific literature?

A: Yes.

Q: Turning to U.S. Trial Exhibit 64315 (no JS number) entitled, Women and Smoking, did you review the 2001 report as part of your investigation in this case?

A: Yes, that addressed women and smoking.

Q: Do the conclusions in that report form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is that report a reliable authority in the published scientific literature?

A: Yes.

Q: Turning to U.S. Trial Exhibit 88847 entitled, The Health Consequences of Smoking, did you review this 2004 report as part of your investigation in this case?

A: Yes. I was the Senior Scientific Editor for this report, which covered the full range of effects of active smoking. It found a number of diseases to be caused by smoking that had not been previously listed: for example, cataract, cervical cancer, and acute myeloid leukemia.

Q: Do the conclusions in that report form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is that report a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor Samet, directing your attention to U.S. Trial Exhibit 64066 (Samet Reference Exhibit 29), the 1986 International Agency for Research on Cancer monograph on smoking, would you identify that for the record?

A: This is a copy of a monograph entitled Tobacco Smoking, Volume 38, it is in a series entitled IARC, International Agency for Research on Cancer, World Health Organization, on the evaluation of the carcinogenic risk of chemicals to humans, published in 1986.

Q: Did you review the 1986 IARC monograph as part of your investigation in this case?

A: Yes, I did.

Q: Do the conclusions in that monograph form part of the basis of the opinions that you hold in this case?

A: Yes.

Q: Is this study a reliable authority in the published scientific literature?

A: Yes.

Q: Directing your attention to U.S. Trial Exhibit 86746 entitled, Tobacco Smoke and Involuntary Smoking, would you identify that exhibit for the Court?

A: This is the monograph prepared by the IARC and published in 2004, based on a meeting in 2002.

Q: Did you review that monograph as part of your investigation in this case?

A: Yes.

Q: Do the conclusions from that monograph form part of the basis of the opinions that you hold in this case?

A: Yes, the IARC monograph published in 2004 was based on a 2002 meeting that I chaired.

Q: What are the topics of that monograph?

A: It covers both active smoking and involuntary smoking.

Q: Do you consider this 2004 IARC publication to be a reliable authority in the published scientific literature?

A: Yes.

Q: Doctor Samet, has the Surgeon General of the United States provided any guidance or criteria to determine whether smoking is a cause of disease?

A: Yes. The 1964 Surgeon General's report set out a set of criteria for evaluating evidence on smoking as a cause of disease. The 2004 report also reviewed these criteria and further addressed the topic of causality.

Q: Doctor, directing your attention to U.S. Exhibit 17132 (JS030), entitled "Causal Criteria," would you explain that exhibit to the Court?

A: Yes. This exhibit quotes text on page 20 of the 1964 Surgeon General report. It says, "Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or the effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:

The consistency of the association

The strength of the association

The specificity of the association

The temporal relationship of the association

The coherence of the association

These criteria were utilized in various sections of this Report. The most extensive and illuminating account of their utilization is to be found in Chapter 9 in the section entitled 'Evaluation of the Association Between Smoking and Lung Cancer.'"

Q: Doctor, would you explain for the Court the causal criteria that are listed in this exhibit and explain what each one means, beginning with the first one?

A: Yes. "Consistency" refers to the consistency of findings for replication of the study; that is, have multiple studies each shown the same finding? Have the results been consistent in different populations and when carried out by different investigators?

"Strength" refers to the magnitude of the relative risk; how strong are the relative risk values? Higher relative risk values are more difficult to explain by the actions of other factors, that is, uncontrolled-for confounders. Under strength we also look at dose-response. Does the relative risk rise as the degree of exposure to cigarette smoking increases, the number of cigarettes per day, or the number of years that someone has been smoking?

"Specificity" is not highly relevant to smoking. Specificity refers to a unique relationship between smoking and disease; that is, does smoking only cause one disease, and is that disease only caused by smoking?

Outside of the infectious diseases, there are few examples of specificity. For example, in regard to specificity for lung cancer in the United States, we know that smoking is the predominant cause of lung cancer, but there are other causes, such as asbestos. For heart disease,

smoking is a major cause but there are other causes. Thus specificity is not found with regard to smoking as the causal evidence is evaluated.

Q: Would you explain the criterion: the "temporal relationship of the association?"

A: The "temporal relationship" simply means that smoking should come before the effect; that is, there should be a proper ordering of the cause-effect relationship. People begin smoking. At some point after they have smoked, they have been exposed to the disease-causing agents in the smoke and subsequently disease occurs. As we look at the risks of smoking-caused diseases, the Court will see that most of the smoking-caused diseases take some time to develop. People smoke first, and the diseases develop later, fulfilling the criterion of a proper temporal relationship.

Q: Would you explain the last criterion to the Court, "the coherence of the association?"

A: By "coherence," we mean does the evidence fit from different lines of information? For example, have disease rates increased in the population in parallel with smoking prevalence? What do we know from experimental work? What do we know about the biological basis by which smoking could cause the disease? What happens when people stop smoking; do the disease risks go down? Thus, under coherence, we bring together all the lines of information and consider them together. Alternative explanations are considered. Are there any plausible alternatives to smoking being the cause of disease?

Q: Doctor, how are these criteria used?

A: These criteria have been applied periodically by the Surgeon General in looking at the evidence on smoking and disease. They are guidelines by which the evidence is evaluated and a

determination is made whether the evidence is sufficient to warrant the conclusion that smoking caused disease, a causal conclusion.

Q: Do all of the criteria have to be met for a causal conclusion to be warranted?

A: No, all the criteria do not have to be met. In fact, that point is expressed in this exhibit: all criteria should be utilized, no one of which is an all-sufficient basis for judgment, nor does each criteria need to be met. However, proper temporality is mandatory.

Q: Did you rely on these criteria in forming your opinions in this case?

A: Yes, I did.

Q: Doctor, how often does the Surgeon General apply these criteria to evidence of smoking and disease?

A: Although a Surgeon General's report is issued almost every year, each report is not a progressive updating of the prior reports. For example, cancer was the topic of the 1982 report, but cancer has not been systematically reviewed subsequently, until 2001 and 2004. Heart disease was the subject of the 1983 report but it has not been systematically reviewed subsequently until 2004. Evaluation of the evidence on specific diseases has been episodic rather than done in each report, looking at all the evidence for each disease.

Q: The 2004 Surgeon General's report reviewed the full scope of the evidence on active smoking?

A: Yes, the 2004 report provides a full updating. Uniform language was used to describe the strength of evidence for causality for all of the health consequences of active smoking.

Q: Doctor, would you tell us what appears on U.S. Exhibit 17133 (JS031), which is titled "Causal Criteria - 1964 Surgeon General's Report?"

A: Yes. This exhibit summarizes the criteria that were in the previous exhibit which represented page 20 of the 1964 Surgeon General's report.

Q: Using lung cancer as an example Doctor Samet, would you explain to the Court how these criteria are used to determine causality. Let's start with the first criteria: is there evidence of "consistency" with respect to lung cancer?

A: Lung cancer has been studied over and over again in epidemiological studies across the decades. These have been carried out in many countries. The findings of these studies have shown over and over again that the relative risk of lung cancer is increased substantially by cigarette smoking.

Q: Turning to U.S. Exhibit 17134 (JS032) entitled, "Relative Risk of Lung Cancer, Current Smokers vs. Never Smokers: Men" could you use this exhibit to explain the application of this criteria to the Court?

A: This exhibit summarizes the findings of numerous studies in the Surgeon General's computerized database. These relative risk values are included in the studies that are in the over 1600 studies entered into the computer database. These are the relative risk values taken from those studies. We see the relative risks of the epidemiological studies for lung cancer in men, we're seeing the relative risks of lung cancer in these studies included in the database based on the year, referring to the year in which the study was reported across the bottom, and you can see the planes here, 1X being the relative risk for never smokers, and then just for reference there is a plane set at a relative risk of 10, a one thousand percent increase, and then each bar represents the findings of an individual study. So you can see that all of these points are above one, some are quite high, and a number are well above the plane showing a relative risk of ten.

Q: These are some of the studies that you have reviewed?

A: Correct.

Q: Turning to U.S. Exhibit 17136 (JS033) entitled, "Relative Risk for Lung Cancer, Current versus Never Smokers: Women" what does that exhibit show?

A: This exhibit looks very similar, showing the relative risk for lung cancer in women, looking at studies published from 1950 on. There are fewer studies of women than of men. These are the relative risk values, one being the relative risk reference value for never smokers, and the Court can see the plane set at 10 just to give the Court a fix on these relative risk values.

Q: What is the source of the information in this graph?

A: The source of the information in this graph is the studies that have been reviewed and abstracted with their findings into the Surgeon General's computer database.

Q: Turning now to the "strength of the association" criterion, what evidence is there of strength of association with respect to lung cancer?

A: Looking at the relative risk values for men, the Court can see values that range up to 20 or more. The Court can see many relative risk values rise above ten, some values as high as 20, comparing the relative risk in smokers to relative risk in never smokers. These are very strong increases in relative risk. The Court should note the large number of studies and some tendency for the relative risks to rise since the 1950s.

Q: Doctor, directing your attention to U.S. Exhibit 17138 (JS034), entitled "Relative Risk of Lung Cancer by Cigarettes Smoked Per Day: Current Smokers Versus Never Smokers: Men," would you tell the Court the source of the data?

A: Yes. The graph summarizes the data that have been abstracted from some of the most important epidemiological studies on smoking and lung cancer. These graphs show the findings

in those publications as they have been abstracted and entered into the Surgeon General's database. Based on that database, I have directed the preparation of this graph, which shows the relative risk values for individual studies included in the database by the number of cigarettes smoked per day.

Q: Is this graph based on the studies that you have reviewed for purposes of your investigation in this case?

A: That's correct.

Q: Are these reliable authorities in the published scientific literature?

A: Yes.

Q: Would you tell us what is on the two axes of the graph?

A: Yes. On the horizontal axis, the X axis, is the number of cigarettes smoked per day. You can see, going from zero, which of course is the never smokers' number of cigarettes smoked per day, out to 60 cigarettes per day for heavy smokers. The vertical axis, the Y axis, is the relative risk of lung cancer in the current smokers in these studies compared to the never smokers at the various levels of cigarettes smoked per day.

Q: What do the dots represent, doctor?

A: Each square represents the dose-response relationship observed in an individual study. I have taken the dose-response relationship, across categories of smoking and plotted a line connecting the points. The lines are just connecting the dots of the individual study estimates of relative risk for each level of cigarette smoking.

Q: On this exhibit is each line a study?

A: Each of these lines going from left to right represents the dose-response within an individual epidemiological study.

Q: And what do the dots represent?

A: Each square represents the relative risk value obtained in each study for a particular level of cigarettes smoked per day. Then I have connected the dots to generate the line. The purpose is to show the Court the relative risk values in each study. A single line corresponds, for example, to the relative risks for the Wynder and Graham or the Doll and Hill case-control studies.

Q: What is the significance of the graph?

A: The graph makes a number of key points. First, the Court can see that there are many studies on the graph, and this graph is limited to only those studies that were included in the computer database. We can see that the findings of the studies are relatively consistent. The Court can see that all the lines rise, so that as the dose, number of cigarettes smoked, goes up in each study for the current smokers, the relative risk values go up as well.

The Court can also see that, while there is varying steepness of the lines, the lines all go up; that is, in each study we see a dose-response relationship between the number of cigarettes smoked and the relative risk for developing lung cancer.

Q: Directing your attention to U.S. Exhibit 17139 (JS035), which is entitled "Relative Risk of Lung Cancer by Cigarettes Smoked Per Day: Current Smokers Versus Never Smokers: Women," what is the source of the data in this exhibit?

A: This exhibit is similar to the plot for men in U.S. Exhibit 17138 (JS034). Each of many epidemiological studies has been abstracted and the findings placed on the graph in this exhibit.

Q: What are the axes in this graph?

A: The information is laid out in this graph, just like the last exhibit, with the number

of cigarettes smoked per day on the horizontal, and then on the vertical the relative risk for lung cancer in current smokers of varying numbers of cigarettes per day compared to women who never smoked.

Q: What is the significance of the graph to disease causation?

A: In this graph for women, the Court can also see consistency: the lines for the most part tend to rise with the number of cigarettes that women smoked per day; that is, the relative risk increases with the number of cigarettes smoked per day. The Court can also see the dose-response relationships in these studies. In terms of the strength of the relative risk, the Court should note that many of the values at the upper end of smoking are quite high, a number of the lines even reaching values higher than 30, meaning that the groups of women who smoked most intensely had risk of lung cancer 30 times more than that of women who never smoked.

The values, for example, towards the right, would correspond to the relative risk of lung cancer for women smoking 30 or more cigarettes per day in the individual studies.

Q: With regard to this lung cancer example and the information and studies that you have just discussed, what is your opinion as to whether the causal criteria of consistency and strength have been met?

A: They have. The Court can see that the findings of many epidemiological studies done over time have been consistent. The relative risk values for lung cancer are very strong, very high relative risk values, obviously meeting the criterion of strength. Also, consistently the relative risk for lung cancer in smokers compared to never smokers increases with the number of cigarettes smoked per day. The Court can see the overall similarity of findings in men and women.

Q: Turning to the next causal criteria, specificity. Can you explain to the Court whether that criteria has been met with regard to smoking and lung cancer?

A: I commented on specificity earlier. That criterion is the concept that one factor only causes one disease and that disease is only caused by that one factor. We know that is not true in the case of smoking and lung cancer. First, we know that smoking causes diseases besides lung cancer and second, we know that lung cancer has causes other than smoking.

So in terms of specificity, this criterion is neither met nor is it applicable to this well-worked-out problem of smoking and its causation of lung cancer.

Q: Let's go to the next criterion, which is the temporal relationship. Doctor Samet, can you explain to the Court whether that criterion has been met?

A: Yes. Temporality as listed in U.S. Exhibit 17133 (JS031) refers to the timing: Did smoking come before the lung cancer? The data on smoking, lung cancer and age show clearly that smoking usually begins in adolescence and early adulthood and the smoker may smoke a very long time before lung cancer develops. So when we look at the occurrence of lung cancer in the population, when does lung cancer occur? We do not begin to see lung cancer cases occurring until people reach approximately their thirties or forties, and that would typically be following several decades of smoking. Smoking comes long before lung cancer risk is evident, and then as the effects of smoking come into play in causing lung cancer, the age-related curve of lung cancer occurrence begins to rise. Thus, the causal criteria of temporality is met.

Q: Let's turn now to the fifth and last criterion, which is coherence. What is the evidence of coherence?

A: Coherence refers to convergence of a number of lines of evidence. It includes information on how the numbers of cases have changed over time and whether that change over

time in the number of cases seems to be reflective of the changes in smoking patterns in the population. It would include information on what happens to the relative risk values after smoking cessation. It would include knowledge of how smoking acts to cause lung cancer, the biological mechanisms that come into play. Knowledge of the actions of individual components would also be coherence. Coherence also includes consideration of any plausible alternative explanations to smoking as a cause of lung cancer.

There is now a massive amount of information relevant to coherence for smoking and lung cancer. The evidence ranges from molecular to population levels. We know much about how some tobacco carcinogens damage DNA. At the population level, we see declining cancer rates, in these populations that have had declining smoking rates for some decades, like men in the U.S. In women, the rate of increase is now slowing.

Q: How common was lung cancer at the turn of the 20th Century, Dr. Samet?

A: Lung cancer was seemingly a rare disease at that time, and now it is the most common cause of cancer death in the U.S.

Q: Now Doctor, please turn your attention to U.S. Exhibit 17140 (JS036), which is entitled "Annual Number of Lung Cancer Deaths and Annual Number of Cigarettes Smoked Per Capita (18 Years of Age and Older) in the United States, 1900-2000." What is the basis and the source of information for this exhibit?

A: This information comes from the vital statistics for the United States. We code each death as to underlying cause and this exhibit shows the counts for lung cancer by year. Also, each year the Department of Agriculture reports the per capita consumption of cigarettes in the United States for the total population, smokers and nonsmokers, age 18 and above.

Q: What are the axes for this graph?

A: The bottom axis, the horizontal or X axis, is simply the year, going from 1900 through 2000. For lung cancer deaths, the vertical axis on the right-hand side is simply the number of annual lung cancer deaths on a scale going from zero to 180,000. The vertical axis on the left-hand side is the annual number of cigarettes consumed per capita on a scale going from zero to 4500.

Q: Does the red line represent lung cancer deaths among men and women?

A: Yes.

Q: What does the solid blue line represent?

A: The blue line represents the annual number of cigarettes consumed per capita in the United States.

Q: What is the significance of this graph, U.S. Exhibit 17140 (JS036)?

A: What is apparent from the graph is the progressive rise in deaths from lung cancer in men and women in the United States from 1930 with approximately 2,800 deaths to over 155,000 deaths in 2000. That is just a bit more than a fifty-fold increase. The rise in deaths follows the substantial increase in per capita consumption of cigarettes in the United States. Since 1954 there have been more than 4.3 million lung cancer deaths in the United States.

Q: Doctor, let's discuss another aspect of coherence. Directing your attention now to U.S. Exhibit 17141 (JS037), which is entitled "Relative Risk of Lung Cancer by Number of Years Since Quitting Smoking: Former Smokers Versus Never Smokers: Men," what is the source of the data in this exhibit?

A: In this exhibit the source of the data is the many studies that have been reviewed and abstracted into the Surgeon General's database. This graph shows some of the findings of those studies.

Q: What do the axes of this graph represent?

A: The bottom axis, the X or horizontal axis, is the number of years that people who have stopped smoking remained former smokers, going from zero out to 30. The Y axis, the vertical axis on the left, is the relative risk scale for developing lung cancer in these former male smokers compared to male never smokers. The relative risk for never smokers is marked on the bottom of the graph and extends across the whole bottom of the graph.

Q: What do the dots and lines represent?

A: The dots on this plot, like the dose-response plots, are the findings of individual epidemiological studies, each dot showing the relative risk of lung cancer in male former smokers compared to male never smokers using the number of years quit. On each line, there are dots representing the relative risk values for individuals in the studies grouped by the specific years since quit. For each individual study, the dots or groups of former smokers are connected to show the general pattern of how the relative risk for developing lung cancer drops after people stop smoking.

Q: What does that have to do with the causal criterion of coherence?

A: This is a line of evidence that scientists examine in looking at coherence: what happens when exposure ends. In the previous graph, the Court saw how the number of lung cancer deaths had risen in United States, consistent with the rise of smoking across the 20th century. Now the question is posed: if smoking causes lung cancer, we should also see that when people stop smoking, the relative risk drops. In U.S. Exhibit 17141 (JS037) the Court can see that in fact the relative risk does drop with the time that people have stopped smoking, declining towards the relative risk for never smokers, although in most of these studies the lines remain well above

never smokers for a substantial number of years after stopping smoking. People who have managed to quit smoking still have an elevated risk for developing lung cancer.

Q: Doctor, let's look at the same data for women. Directing your attention to U.S. Exhibit 17142 (JS038), entitled "Relative Risk of Lung Cancer by Number of Years Since Quitting Smoking: Former Smokers Versus Never Smokers: Women," what is the source of the data for this exhibit?

A: As was true for the previous exhibit, the sources of the data in this exhibit are the many studies that have been reviewed and abstracted. This graph shows some of the findings from those studies.

Q: What are on the axes of the graph?

A: This graph is laid out exactly the same way as the previous one for men, but this one is for women. We see the relative risk for lung cancer in former smokers compared to never smokers plotted against the number of years that those women have stopped smoking.

Q: What do the lines and dots represent?

A: The lines represent the results of individual studies of women smokers who have stopped. The dots for the specific groups of former smokers in the studies have just been connected to form the lines, so each line represents the findings of one epidemiological study.

Q: What does the Court see here in terms of relative risk?

A: The Court can see that the relative risks for women former smokers compared to never smokers for developing lung cancer drop with increasing number of years quit, declining from very high relative risk values to somewhat lower values. The relative risks remain somewhat above one, although continuing to decline over time.

Q: The pattern that the Court sees for women is similar to the pattern seen for men?

A: That's correct.

Q: Is this further evidence of coherence?

A: Yes. We would expect that if cigarette smoking is causing lung cancer then the withdrawal of exposure to the carcinogens in tobacco smoke would lead to a reduction in risk, which is what was observed in the studies. Even with relatively long duration of quitting, the risks of lung cancer in former smokers remain higher than those of never smokers.

Q: Doctor, are there explanations other than smoking for what the Court is seeing here?

A: When scientists put the full pattern together, what we saw with the consistency and the very strong risks in smokers, the dose-response, the rise in relative risk in smokers with numbers of cigarettes smoked per day, and the declining relative risks when people stop smoking, I have no alternative explanation to smoking being a strong cause of lung cancer.

For there to be some alternative explanation, we would have to be missing some other factor that was associated with smoking and in fact could cause lung cancer risks at least as high as those we see in smokers or even higher, that would be associated with the number of cigarettes smoked per day, and that when people stop smoking, somehow that factor would stop having any effect. After more than 50 years of scientific investigation, no alternative explanation for these findings, other than smoking has been found. Reaching a causal conclusion may take years as the evidence accumulates and is evaluated, and alternatives to causation are considered.

Q: Doctor, is there any other evidence of coherence with respect to lung cancer and smoking?

A: There are many lines of biological investigation into how smoking causes lung cancer. Scientists are becoming increasingly sophisticated in terms of our ability to understand how the

carcinogens in tobacco smoke act to cause lung cancer. This information is fully covered in the 2004 report of the Surgeon General and the 2004 IARC Report.

There is a well known report, for example, on one of the carcinogens in tobacco smoke, benzo(a)pyrene. In a study that was published in 1996, it was found that the activated metabolite of this carcinogen, the activated carcinogen itself binds to a gene at the very spots where we see mutations in that gene in smokers. This gene, P-53, is a tumor suppressor gene. It suppresses the growth of potentially cancerous cells, and we need this gene, P-53, to do housekeeping with cells that are getting out of line and having precancerous changes. What we find in cancers in smokers is that this gene is frequently mutated, i.e., changed, and we think that the mutated P-53 gene can no longer do its job. The 1996 study showed that in people who do not have lung cancer but who smoke, we can find this activated carcinogen sitting right on the spots in the P-53 gene where we later find mutations in cancers in smokers. This is only one of many studies that scientists are now able to perform with the new techniques of cancer biology and cancer genetics.

Q: Doctor Samet, is the causal criterion of coherence met for smoking being a causal factor in lung cancer?

A: Yes, there is no question that the coherence causal criterion is met.

Q: Doctor, I want to turn now to specifics about the disease of lung cancer. Can you explain to the Court what lung cancer is?

A: By "cancer," scientists mean the development of a tumor or mass of cells that have uncontrolled, unrestrained growth. We think that most cancers originate with one cell which gets out of control, divides and divides and divides until it forms a large mass, perhaps resulting in

local damage. Many cancers can spread throughout the body, a process called metastasis. Lung cancer refers to the cancers that arise in the lung as the primary organ of origin.

Q: Doctor, please turn your attention to U.S. Exhibit 17143 (JS039) entitled, "Tumor Development Occurs Progressively," and explain to the Court what it is seeing in this drawing starting from the left side.

A: This exhibit, moving from left to right, depicts in one panel how a normal cell that has genetically changed would develop sequentially into a cancer, moving through stages. The first stage is called hyperplasia, that is, an area of overgrown cells. The next stage of development is called dysplasia involving the further growth of abnormal cells. Moving on, the process advances to form what scientists call an in situ cancer. That phrase refers to a cancer that is still localized in the organ of origin. As the Court can see in this exhibit, the cancer is sitting above the brown band which is one of the membranes in this surface.

As the cancer continues to develop and as its behavior becomes more aggressive, it would invade beyond the superficial lining of the surface, for example the lining of the lung in the case of lung cancer, and cause local damage, perhaps invade blood vessels, and as is shown here, metastasize or spread throughout the body and go to distant sites, like the brain or the bones.

Q: What color are the cancer cells in U.S. Exhibit 17143 (JS039)?

A: The cancer cells are shown in purple.

Q: Can these cancer cells spread to other sites?

A: Yes, they can.

Q: Can you describe that process for the Court?

A: Yes. The mass of cancer cells may invade locally and spread through the lung and through the chest wall. The cells can also enter into the bloodstream and spread to sites outside the lung, a phenomenon known as metastasis. Some of the common sites for lung cancer are the brain, the bone, the spinal cord, the liver, the adrenal glands, and the sac around the lung.

Q: Doctor, I want to direct your attention to U.S. Exhibit 17144 (JS040) entitled, "Brain with Cancer Metastases," what is it that the Court can see in this exhibit?

A: This is an accurate depiction of the appearance of a brain with cancer metastases in it. The Court is looking at an image of the brain obtained with a CT or CAT scan showing tumor masses in the brain. Each one represents a typical metastasis, and what the Court can see in this darker area surrounding each one is the swelling that often occurs around a metastasis in the brain. Of course, having large masses in the brain like the ones shown in this exhibit may severely affect the functioning of that part of the brain. One of the common presentations of lung cancer is with metastasis to the brain.

Q: What are the general symptoms of lung cancer?

A: There are a variety of general symptoms of lung cancer. One is weakness, loss of energy. There may be pain from sites that have been invaded by the cancer or have metastases growing in them. There may be the many possible symptoms of having cancer spread into the brain and interfere with brain function. There are metabolic syndromes, the sodium being too low, the calcium being too high, and other problems. So the face of lung cancer is varied. There are many symptoms associated with its general manifestations.

Q: Doctor, what are the local symptoms of lung cancer?

A: I think about the local symptoms from lung cancer in two ways, those that just come from the tumor itself, and those that come from its spread.

A tumor growing within the lung may cause a cough. The surface of the cancer may erode and there may be bleeding. For that reason, smokers with lung cancer often present with coughing up of blood. They may have chest pain if the cancer has eroded into the surrounding tissues, for example into the esophagus, the swallowing tube, or into the ribs or other structures. They may have pneumonia because the esophagus is blocked and they cannot clear the secretions behind the tumor. In this circumstance, bacteria find a fertile ground for growing and causing pneumonia that may be very difficult to treat.

Q: How is lung cancer diagnosed?

A: Today typically lung cancer is diagnosed in several ways. One is by bronchoscopy, which is done with a flexible tube called the fiber-optic bronchoscope. The tube is just passed down through the nose, the mouth, the voice box and into the lung. There the operator can visualize any lung cancers, take biopsies from the surface to establish the diagnosis, and examine the extent of the tumor. This is something that, unfortunately, I've done many, many times, seeing many, many cancers.

Another way that we make the diagnosis now is by passing a small needle into the tumor mass, and taking some cells or a small biopsy. These are examined under the microscope. Some cancers are still diagnosed at surgery.

Q: What is the outcome of lung cancer?

A: The prognosis for lung cancer is approximately 14 percent five-year survival. For those practicing pulmonary medicine, we frequently face the very difficult task of doing a bronchoscopy, identifying the cancer, and talking to our patients an hour or two later, after they have awaken from sedation, and telling them what lies in store for them. This is never easy.

Q: Doctor, what are the different types of lung cancer?

A: There are four principal types: small-cell carcinoma, squamous-cell carcinoma, adenocarcinoma and large-cell carcinoma.

Q: Turning your attention to U.S. Exhibit 17145 (JS041) entitled "Small Cell Carcinoma of the Lung," which is a depiction of a small-cell carcinoma, can you tell the Court whether that picture accurately portrays a small-cell carcinoma?

A: Yes, this is an accurate representation of the typical microscopic appearance of a small cell carcinoma of the lung.

Q: Doctor Samet, can you describe the appearance of small-cell carcinoma as can be seen by the Court in this exhibit?

A: Yes. Small cell carcinoma is called that because under the microscope; the cancer cells are the clumps of small dark cells which are relatively uniform; they have small dark centers or nuclei. In this exhibit, the Court can see what a physician would see under a microscope when looking at tissue from such a cancer.

Q: Where in the lung is small-cell carcinoma typically found?

A: Small-cell carcinoma is a cancer that tends to arise in the tubes of the lung, in the initial major airways, the bronchi, often towards the upper lobe of the lung. For that reason, the tumor tends often to present with signs of blockage of one of the tubes, the bronchi. But unfortunately this cancer also tends to spread early and quickly. Small cell carcinoma is considered to be metastatic at the time of diagnosis by definition. Beneath where the trachea divides into the two bronchi are lymph nodes. The lymph nodes are often a site to which cancer spreads.

Q: Doctor Samet, what are the symptoms of a patient presenting with small-cell carcinoma?

A: The symptoms that arise from small-cell carcinoma would likely reflect what is happening locally. The cancer often arises in an airway, and blocks the tube. There might be cough, coughing up blood, chest pain, then later signs from the spread of the cancer. This cancer, as I have said, tends to spread early and aggressively, so some of the common sites affected are often the brain or the bones, where smokers would experience bone pain. The adrenal glands may become filled with cancer and smokers actually develop an insufficiency of the adrenal glands. There may just be generalized weakness. There are also some very special metabolic problems that may occur with this type of cancer.

Q: What proportion of lung cancer cases are small-cell carcinoma?

A: This type of lung cancer accounts for approximately 15 - 20 percent of all cases of lung cancer in the United States.

Q: Doctor, what are the other primary types of lung cancer?

A: The other three types of lung cancer are often referred to collectively as non-small-cell cancer, because clinically there's an important distinction in treatment for non-small-cell versus that for small cell. The other three principal types of non-small-cell lung cancer are: squamous-cell cancer, adenocarcinoma, and large-cell carcinoma.

Q: Doctor, please direct your attention to U.S. Exhibit 17146 (JS042). Is that an accurate depiction of a squamous-cell carcinoma?

A: Yes. This exhibit is an accurate representation of the typical microscopic appearance of squamous cell carcinoma of the lung. In this exhibit, the Court can see what a physician would see under a microscope when looking at tissue from such a cancer. The picture is quite different from small cell. The cells are much larger, for example.

Q: What percentage of all lung cancers is squamous-cell?

A: This type of lung cancer, squamous-cell, accounts for approximately 20 to 25 percent of lung cancer cases at present.

Q: Where does it arise in the body?

A: This type, like small-cell, tends to arise very centrally within the lung, often within the first three to four to five generations of the bronchi as they branch in the lung. This cancer also tends to be somewhat nearer to the trachea than some of the other types.

Squamous-cell cancers tend to arise very early in the divisions of the airways as they move out to the alveoli. So what a physician might see through a bronchoscope is a tumor mass actually obstructing the airway. This blockage could lead to symptoms such as cough or coughing up blood. On a chest x-ray, a physician typically would see a tumor mass sitting centrally within the lung.

Q: Doctor, another type of non-small cell carcinoma is adenocarcinoma. Can you turn to U.S. Exhibit 17147 (JS043) entitled, "Adenocarcinoma of the Lung." Is that an accurate representation of an adenocarcinoma?

A: Yes. This exhibit is an accurate depiction of the typical microscopic appearance of adenocarcinoma of the lung. In this exhibit, the Court can see what a physician would see under a microscope when looking at tissue from such a cancer. The cancer cells are organized and contain mucous-like material.

Q: Can you tell the Court where adenocarcinoma is typically found?

A: Unlike the small-cell and the squamous-cell, carcinoma, adenocarcinomas tend to arise more out to the periphery of the lung.

Q: Doctor Samet, what percentage of lung cancers is represented by adenocarcinoma?

A: This type of lung cancer has been rising in frequency over approximately the last 25 or 30 years and now accounts for about 30 percent or more of lung cancers in the United States. It is the most common type.

Q: What are the symptoms of adenocarcinoma?

A: The symptoms are varied. One presentation is identification of a mass on an x-ray. But more often symptoms come from local problems: cough, coughing up blood, for the other types of cancer. These cancers can erode through the lung and actually enter the sac, the pleura that surrounds the lung. They can actually spread beyond that and invade into the ribs and chest, causing chest pain, the appearance of a mass, or like the other types of cancer, they can spread to distant sites. In that case, another presentation would be with metastasis to the brain or perhaps to the bones.

Q: Doctor, could you turn to U.S. Exhibit 17148 (JS044) entitled "Large Cell Carcinoma of the Lung," is that an accurate depiction of a large-cell carcinoma?

A: Yes, it is. This exhibit is an accurate representation of the typical microscopic appearance of large-cell carcinoma of the lung. In this exhibit, the Court can see what a physician would see under a microscope when looking at tissue from such a cancer. This cancer is named after the relatively large size of the cancerous cells.

Q: What percentage of lung cancers is represented by the large-cell carcinoma?

A: The large-cell is less frequent than the other types that I have been talking about. Large-cell accounts for 10 percent or less of all lung cancers.

Q: Where is large-cell carcinoma typically found?

A: Large-cell carcinoma tends to be somewhat peripheral, like adenocarcinoma, and it tends to present as a large mass, although the name of the tumor comes from its cellular appearance of having large cells, not from the large mass with which it usually presents.

Q: Doctor, you said that large-cell carcinoma tends to be peripheral. What do you mean by "peripheral?"

A: For example, with the small-cell and squamous-cell carcinomas, there is typically a mass centrally next to where the lung originates, next to the heart. With this type, large-cell carcinoma, the tumor is more out towards the edge of the lung, towards the periphery of the lung.

Q: Doctor, are there curative treatments for lung cancer?

A: That depends on the type of lung cancer and the stage at which the lung cancer has been diagnosed.

Q: What are the curative treatments for small-cell carcinoma?

A: As I said before, in thinking about treatment clinically, physicians divide lung cancer into small-cell and non-small-cell. This division is made because small-cell is considered to be metastatic at the time of diagnosis. Over the years through clinical experience physicians have learned that this is a very aggressive tumor; it spreads very early in its natural history, early in its course, because the cells are so aggressive. The cancerous cells move throughout the body, so that surgery cannot be the right treatment, taking out the cancer mass in the lung still leaves all these cells that are present throughout the body, even if they cannot be seen. So treatment for small-cell cancer of the lung is limited to a combination of chemotherapy and radiation. Current treatment for small-cell cancer would include very intensive chemotherapy. Then, because the brain is one of the sites to which these cells spread, the treatment protocol also usually involves

whole-brain irradiation. This is a very difficult course including chemotherapy plus irradiation of the brain; only a small percentage of patients survive five years with this disease.

Q: What side effects are typically associated with chemotherapy?

A: Courses of chemotherapy are very demanding. They make patients sick, they make their hair fall out, and there are a variety of potentially serious complications. The treatment knocks down the body's immune responses. Patients having chemotherapy are at risk for infection, bleeding, and many other complications.

Q: What are the typical side effects from radiation?

A: Patients receiving brain irradiation are obviously affected – they are sick. The swelling of the brain that can occur during the radiation can affect brain function.

Q: Doctor Samet, let's turn to curative treatments for non-small-cell carcinoma. What is the typical course of treatment?

A: Unlike small-cell carcinoma, the typical approach is surgery, so that for those persons with cancer that is limited at the time of diagnosis to one area of the lung, it may be possible to surgically resect the involved part of the lung; that is, take out that piece of the lung. Or sometimes for larger tumors, or depending on the location, it may be necessary to take out the entire lung. That procedure is called pneumonectomy.

Q: Doctor, what special concerns, if any, can arise in performing surgery on a lung cancer patient who is a smoker?

A: This is very serious surgery for any patient. Any time a surgeon opens the chest cavity and begins to remove lung tissue, this is high risk although, fortunately, with modern surgical techniques, risks are lower than before.

The concern in operating on individuals who have smoked is that smokers are at greater risk for complications. This was one topic of the 2004 Report of the Surgeon General. For example, when a physician considers taking out one lung, the surgeon and the physician have to know how affected the remaining lung might be by COPD because smokers are also at higher risk for both COPD and heart disease. For this reason, there may be greater risk for complications following surgery from coronary heart disease if the smoker's remaining lung is also afflicted with COPD.

Q: Doctor, can you tell me whether radiation is ever used with non-small-cell carcinoma?

A: Sometimes radiation is used for very localized non-small-cell carcinomas, particularly adenocarcinomas, in individuals who may not be able to have surgery, perhaps because their lungs are already damaged from smoking. But more often, radiation is reserved for treatment of the distant spread and local complications of the cancer, rather than any attempt to actually cure the cancer.

Q: Doctor Samet, you have been talking about curative treatment. Are there other kinds of treatment for those who cannot be cured?

A: For those who cannot be cured of lung cancer, which constitutes the majority of lung cancer patients, there are a variety of what physicians call palliative treatments. These are treatments to try and maintain the quality of life for as long as possible for those who have the cancer. These are treatments to help control pain and other complications of the lung cancer, its spread, and local complications. Chemotherapy is also being used and there are a few promising therapies.

Q: You used the word "palliative." What do you mean?

A: There are a variety of different types of therapies that might be needed to assure comfort to the extent possible. For example, to treat a blocked bronchus with pneumonia behind it, radiation might be used in an attempt to open up the passage. For someone with bone pain from metastasis, radiation might be used in an attempt to destroy the tumor that is within the bone. Pain control is a very important part of the care for the lung cancer patient, often requiring very skilled use of pain-relieving medications; sometimes, towards the end, the use of continuous IV, that is, intravenous, narcotic drips to maintain pain relief and allow the individual with lung cancer to maintain themselves in relative comfort. Then, because there may be so many other complications from the disease, pneumonia, difficulty eating, depression – a variety of supportive care measures may be needed.

Q: Can this type of care require entry into a hospice or a nursing home?

A: Yes. Very often, as persons with lung cancer become more ill, they may need a level of care that is not possible in the home. Such patients might enter a hospice program, or they may go to a nursing home so that they can have the full-time care that is necessary to keep them relatively comfortable.

Q: Doctor, what are the survival rates for lung cancer?

A: Right now in the United States, the five-year survival is around 14 – 15 percent; that is, of 100 people who are diagnosed with lung cancer, five years later about 15 or so, approximately, will be alive.

Q: What is the leading cause of cancer death in men in the United States today?

A: Lung cancer.

Q: What is the leading cause of cancer death in women in the United States today?

A: Lung cancer.

Q: How many people died in 2001 from lung cancer?

A: There are now approximately 160,000 deaths per year in the United States from lung cancer. The figure for 2001 was 156,000 and the preliminary figure for 2002 is over 158,000.

Q: How many people died in the United States in 1950 from lung cancer?

A: Approximately 18,000.

Q: What is that increase?

A: An approximately eight-fold increase.

Q: Doctor, when did the Surgeon General of the United States first conclude that smoking is a cause of lung cancer?

A: There was a conclusion in 1964. If the Court looks at U.S. Exhibit 17177 (JS046A), the Court can see a summary of all the Surgeon General's causal conclusions with regard to lung cancer from 1964 to 2004. This table also includes the causal conclusion that IARC announced in 2002.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do

you have an opinion to a reasonable degree of scientific certainty that smoking cigarettes causes lung cancer?

A: Yes, smoking causes lung cancer.

Q: Doctor, is there any other disease that is caused by smoking cigarettes that has a relative risk comparable to lung cancer?

A: There are several, most notably chronic obstructive pulmonary disease or COPD.

Q: What is that disease?

A: As I stated earlier, this is an irreversible disease that reflects years of accumulated damage to the lung with development of emphysema and scarring.

Q: Can you describe COPD in more detail?

A: Chronic obstructive pulmonary disease is the name now given to what in the past had been called emphysema, or chronic bronchitis. I'm referring to the irreversible damage to the lung that occurs in a substantial proportion of smokers.

As this disease develops smokers lose more lung function than would occur with natural aging. That is because smoking is causing their lungs to develop emphysema, which means that the alveolar sacs are becoming destroyed and widened, and the lung, instead of having many alveolar sacs, develops larger air spaces which trap air. It loses its elastic properties so that there is difficulty in the lung emptying itself of the air that comes in. Its properties become more like those of a paper bag than those of a balloon.

The very small airways that go out to the alveoli are damaged, becoming thickened and scarred. The end result is that the person who is developing COPD or has COPD loses the ability to move enough air in and out of the lungs to keep up with the normal demands of life. As we do our activities, some demand more breathing: for example, carrying groceries in from the car,

exercising, or mowing the lawn. Persons who develop this disease lose that reserve, and in fact, toward the end of the disease, they may become so limited that activities the rest of us take for granted, like being able to take our clothes on and off, or even to eat, become too demanding in terms of the breathing capacity. COPD refers to this permanent damage to the lung.

Q: What are the treatments for COPD?

A: Well unfortunately, once the disease has developed, this damage to the lung is largely irreversible, so simply stopping smoking does not provide anything more than a small benefit for some of the smokers. The treatment involves some medications that may have benefit, and for this purpose physicians use some of the same medications that are used with asthma.

Another very important treatment, and one that does help the person who has COPD, is oxygen therapy. But for those persons who are more severely affected by the disease, physicians usually would prescribe continuous oxygen therapy to try and keep the blood level of oxygen where it should be, because the disease will have lowered the level of oxygen in the blood. This is the principal proven treatment.

There are some other therapies that have been tried and tested involving surgery, for example, but the mainstays of treatment are oxygen, using some drugs that are very much like the drugs used for asthma, and working with people who have this disease to try and provide support and help them to maintain their daily activities as much as possible.

The disease has a long course, so people who have been diagnosed with the disease may be under treatment throughout their lives. During that time they will be receiving drugs, and perhaps oxygen. They may also be hospitalized because they're vulnerable to the chest colds and respiratory infections that we all normally have. But for the person with no lung reserve, those

illnesses often result in hospitalization and some persons may need a mechanical ventilator (breathing machine) to stay alive.

Q: How common is COPD?

A: It is not uncommon. Surveys, that is, studies where researchers go to communities and try to understand how common the disease is, show that perhaps several percent of adults have this disease. Now, there are approximately 80,000 deaths a year that are attributed to COPD.

Q: Did you conduct an investigation of the published scientific literature regarding whether cigarette smoking causes COPD?

A: Yes, I did.

Q: Did you look at the Surgeon General's reports on this issue?

A: Yes, I did.

Q: Did you investigate whether COPD met the causal criteria set out by the Surgeon General?

A: Yes, I did.

Q: Let's address the consistency and strength criteria. Doctor, directing your attention to U.S. Exhibit 17150 (JS047.1-A) entitled, "Relative Risk of COPD, Current Smokers versus Never Smokers: Men," can you explain the significance of this exhibit?

A: Yes. This chart is like those that we saw earlier concerning lung cancer and summarizing the results of the various epidemiological studies in the Surgeon General's database. Remember these are relative risk values. One is the value for never smokers. We are looking at information for men, describing the relative risk for current smokers compared to never smokers for developing COPD. And looking at the data, the studies go from the 1950s to the present. As we saw earlier, the plane has been set at one, the value for never smokers. Just for reference, ten or

a one-thousand-fold increase in risk is shown on this plane. And you can see the results of a number of individual epidemiological studies, all consistently showing increased risk, some showing very, very strong risks, well above ten, or the 1,000 percent mark.

Q: Can you tell us whether there is a trend with respect to relative risk from the years summarized on U.S. Exhibit 17151 (JS047.1-A)?

A: Well I think if there is a general trend from 1955 to 2000, it would be that over time we have seen a rise in these relative risk values.

Q: Doctor, could you now turn to U.S. Exhibit 17150 (JS047.1) entitled, "Relative Risk of COPD by Cigarettes Smoked Per Day, Current Smokers vs. Never Smokers: Men." What is the source of the data for this exhibit?

A: This exhibit is based on the epidemiological studies that have been included in the Surgeon General's database of studies on COPD.

Q: Doctor, first of all, tell us what this graph is.

A: This graph is similar to the graphs in U.S. Exhibit 17138 (JS034) summarizing the findings of individual epidemiological studies of men. Each dot shows the relative risk values comparing smokers smoking different numbers of cigarettes per day, as shown on the horizontal axis, compared to never smokers. The dots from each study are connected by lines. All the lines start at one, which is the relative risk value for never smokers.

Q: Is there a trend here or some significance to the direction of the lines as the number of cigarettes per day increases?

A: There's an outlying line or two, we sometimes see a little bit of variation in the results of studies. Almost all of the lines show an upward trend of increasing relative risk for COPD with the number of cigarettes smoked by these men.

Q: Doctor, could you now turn to U.S. Exhibit 17153 (JS047.2), titled "Relative Risk of COPD by Cigarettes Smoked Per Day, Current Smokers versus Never Smokers: Women." Can you tell me the source of this graph; that is, the source of the data in this graph?

A: The source for this graph is information contained in the 2004 Surgeon General's database.

Q: Please describe the two axes of the graph.

A: This graph is very much like other graphs that we have seen. The vertical axis showing the relative risk for COPD comparing current smokers to those who have never smoked, the horizontal axis is the number of cigarettes smoked per day. And again, each line corresponds to one epidemiological study, the findings of one epidemiological study.

Q: Can you tell us, basically, what is depicted on the graph itself.

A: We see the general rise of the relative risk values for COPD in women for those who currently smoke by the number of cigarettes smoked per day. So with each increase, for example, in this study in the number of cigarettes smoked per day by the participating women, the relative risk rises.

Q: Doctor, let's turn to U.S. Exhibit 17154 (JS047.2A) entitled "Relative Risk of COPD, Current Smokers versus Never Smokers: Women," can you explain what this exhibit depicts?

A: This is another chart showing the relative risk values for current smokers compared to never smokers for COPD in women over the time. The Court can see that there are fewer bars on this figure than in some of the other exhibits. The fact that there are fewer bars just means that there have been fewer studies of women and COPD.

But even though there are few studies, the Court can see the consistency among these studies in all showing increased relative risk for current smokers compared to never smokers in women.

Q: Are the studies that are depicted in this graph found in the Surgeon General's 2004 database?

A: Yes, they are.

Q: Doctor Samet, let's talk about the criterion of specificity. Please define that term and explain whether that criterion been applied by you to the available scientific evidence regarding COPD?

A: Specificity in the Surgeon General's criteria refers to the idea of a very specific link between some exposure, smoking, and disease; that is, smoking only causes one disease and that disease is only caused by smoking. As I mentioned earlier, that does not apply very well to smoking which causes many diseases, and some of the diseases caused by smoking have a number of other causes.

Now for COPD in the United States, smoking is far and away the predominant cause. At this point some of the other causes, serious childhood infections, for example, or some very high-level industrial exposures, are very rare, fortunately. So by far, the substantial majority of the cases of COPD are caused by cigarette smoking.

Q: Can you tell me whether the criterion of temporality is met by the evidence here?

A: Yes. Temporality means that smoking should come before the development of the disease. In the case of COPD, this is a disease that takes a number of years of smoking before it occurs. The lung is a remarkable organ with a great deal of reserve, and that reserve has to be eroded away by the damage caused by years of smoking before this disease develops. So typically the disease is rarely seen before age 40, except under very unusual circumstances, and

we begin to see, as clinicians, persons presenting with this disease perhaps in the decades of the fifties and beyond. So at that point the smoker may have been smoking for 30 or 40 years. So temporality for COPD is clearly met here. There is a substantial period of smoking before the disease develops.

Q: Let's talk about the final criterion, which is coherence. What evidence is there of coherence?

A: There are a number of lines of evidence to think about with regard to coherence. First, COPD has become a much more common disease. The number of deaths from COPD is rising still. We've seen a rise in this disease approximately parallel but lagging behind the way that smoking began earlier in the last century.

We also have an in-depth knowledge of the ways in which smoking causes COPD. The 2004 Report of the Surgeon General covers knowledge of mechanisms. This is a disease that arises because various factors that can damage the lung in smokers are out of balance with factors that protect the lung against injury. There are enzymes that are normally formed within the lung to protect it against bacteria and particles. Some of the normal control mechanisms for these enzymes are suppressed by smoking. The result is an imbalance in the direction of lung injury.

In the lungs of smokers, there are many inflammatory cells. These are cells that themselves secrete products that can damage the lung. The lungs of the smokers are primed for injury with increased numbers of these cells, and it's this unchecked injury going on year after year as the smoker smokes that can lead to irreversible damage.

We also have other evidence. There have been many studies involving observations on how lung function changes over time in smokers and non-smokers. All of us, as we age,

somewhere beyond about age 30 begin to progressively lose some lung function. But as I said, the lung is a remarkable organ, with substantial reserve, and so those of us who don't smoke can tolerate that loss. But smokers lose lung function at a faster rate, some at a very fast rate, so that by age 50 or perhaps beyond they begin to run out of reserve, and that's when COPD develops.

Physicians know that if smokers are advised to stop smoking early enough and if they stop smoking, the decline in lung function can be reversed. But when physicians typically find somebody with COPD, it's usually too late for smoking cessation to have much impact on their level of lung function.

Q: Doctor Samet, in your prior response you mentioned lung function and its decline. What do you mean by that?

A: By "lung function," I'm referring to tests of how well the lung is working. The test that we most often do is simply to ask people to take a deep breath, fill their lungs up, and blow all the air out as fast as they can. Using a machine, we measure how much air is blown out, the total, and how fast the air comes out.

And when I talked about what happens with aging, we lose some lung size and physicians begin to see some slowing of how fast the air actually comes out. So those are the two things that are consequences of normal aging. Now both of those are accelerated in people who smoke; there tends to be a greater loss of lung size and the amount of air that can be blown out, and also there is a greater slowing of how fast the air can be blown out.

So when I talked about the decline in lung function being more in smokers than in non-smokers, I mean that these age declines in how much air the lung holds and can be blown out and how fast it can be blown out are actually worse in smokers compared to non-smokers.

Q: Doctor Samet, looking at U.S, Exhibit 17133 (JS031), entitled "Causal Criteria 1964 Surgeon General's Report," it gives a summary of those criteria. With respect to COPD, which of these criteria have been met by the evidence?

A: Let me go through the criteria. First, consistency. In study after study scientists find that smokers compared to non-smokers/never smokers have increased relative risk for developing COPD, and also consistently, as we looked at many different groups of smokers, we found this increased rate of loss of lung function that I was just talking about.

Strength, the association is strong in the relative risk values in smokers for developing COPD compared to non-smokers; run ten or more, 1,000 percent increase or more. We also see the dose-response, the increasing strength of this relationship as the number of cigarettes smoked per day goes up.

Specificity I talked about before, and I said that for COPD, as for the other diseases we will be talking about, specificity is not directly met. Although again, in the United States at this time, there are very few causes of the disease that I am calling COPD caused by agents other than smoking.

Temporality. People smoke for many years before they develop COPD.

And finally, with regard to coherence, scientists have a great deal of information, the information I talked about on how lung function changes over time in smokers compared to non-smokers. We have evidence that if people stop smoking early enough, the rate of decline lessens so that the former smoker only loses lung function as fast as the never smoker. And, as I said, we have a great deal of understanding of the processes that are actually taking place in the lungs of smokers that lead to the development of COPD.

I also pointed out that this disease, as a cause of death, is rising. Incidence has become more frequent essentially in parallel to the patterns of smoking across the century in the United States. So with regard to coherence, this criterion is also met.

Q: When did the Surgeon General of the United States first conclude that smoking is a cause of chronic obstructive pulmonary disease?

A: There was a conclusion in 1964, when the term used was "chronic bronchitis," and for various terms including chronic obstructive pulmonary disease and chronic obstructive lung disease in 1984. If the Court looks at U.S. Exhibit 17178 (JS046B), the Court can see a summary of the Surgeon General's causal conclusions with regard to this disease.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, your training, your expertise in the science of smoking and health, and your review of the published scientific literature on smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes chronic obstructive pulmonary disease?

A: Yes, smoking causes chronic obstructive pulmonary disease.

Q: Doctor, did you investigate other smoking-caused cancers other than lung cancer?

A: Yes.

Q: What cancers did you investigate?

A: Laryngeal cancer, oral cancer, esophageal cancer, cancer of the pancreas, bladder cancer, kidney cancer and stomach cancer, liver cancer, cervical cancer, and acute leukemia. I have also considered breast cancer, colorectal cancer and prostate cancer.

Q: Are there any cancers, other than lung cancer, which have relative risks of disease caused by smoking comparable to lung cancer and COPD?

A: Laryngeal cancer—that is cancer of the larynx or voicebox.

Q: Can you describe that disease to the Court?

A: Yes. The larynx, of course, is the voice box, so we're referring to cancers in the voice box, typically involving the vocal cords, and sometimes other structures, within the larynx.

Q: Doctor, directing your attention to U.S. Exhibit 17101 (JS002.1), entitled, "Human Bodies – Man and Woman," can you describe to the Court where the larynx is located?

A: Yes. The larynx is in the neck, marking the dividing point between the upper airway and the lung, and it connects to the trachea, which is the tube that brings the air into the lungs.

Q: Can you describe the features of laryngeal cancer to the Court?

A: Yes. The cancers begin to grow in the cells lining the surface of the larynx. Typically an individual who has this cancer might notice that his or her voice become hoarse or changes; he may have cough; he may cough up blood because the tumor itself becomes somewhat irritated, and he might notice a lump in the neck from a spread of the cancer to the lymph glands in the neck.

Q: Could you describe the treatments for laryngeal cancer?

A: Treatment can involve surgery, to remove part of the larynx or to remove one of the vocal cords, depending on the stage of the cancer, the time of diagnosis. It can involve removal of the

entire larynx or voice box, leaving people to need to find other ways to speak, such as esophageal speech or devices. The treatment can also include radiation as a part of management.

Q: Has the Surgeon General of the United States concluded that smoking is a cause of laryngeal cancer?

A: Yes.

Q: When was that causal conclusion first reached?

A: Cancer of the larynx was addressed in the 1964 report. If the Court looks at U.S. Exhibit 17179 (JS046C), the Court can see a summary of the Surgeon General's causal conclusions with regard to this disease from 1964 to 2004, including IARC's causal conclusion announced in 2002.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes laryngeal cancer?

A: Yes, smoking causes laryngeal cancer.

Q: Let's turn now to oral cancer. Could you describe that disease?

A: Yes. "Oral cancer" refers to cancers that arise in the mouth and in the throat. These are cancers that typically present with symptoms related to the growth of a mass of cancer within those areas. People may experience pain, notice a mass, have difficulty swallowing, or, as in the case of cancer of the larynx, notice a lump in the neck because of spread of the cancer.

Q: Can you describe for us the treatments that are used for oral cancer?

A: The treatment is typically surgery, and often very radical surgery to remove the involved cancer, often involving a dissection of the lymph glands of the neck to try and remove any cancer-containing lymph glands. There may be need for major reconstruction, it all simply depends on the stage at which the tumor is found. Radiation is also typically used.

Q: Has the Surgeon General of the United States concluded that smoking is a cause of oral cancer?

A: There was a causal conclusion in 1979. Oral cancer was first addressed in 1968, and the report stated, "Cigarette smoking is a significant factor . . . in the development of cancer of the oral cavity." If the Court looks at U.S. Exhibit 17180 (JS046D), the Court can see a summary of the Surgeon General's conclusions with regard to this disease from 1968 to 2004, including the causal conclusion announced by IARC in 2002.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes oral cancer?

A: Yes, smoking causes oral cancer.

Q: Doctor, moving to esophageal cancer, could you describe that disease to the Court?

A: The esophagus, of course, is the tube that connects the mouth and throat to the stomach. It passes through the chest, behind the heart. Esophageal cancers arise in the cells that line the esophagus, and symptoms occur when a mass of cells has grown big enough, to cause symptoms: pain on swallowing, difficulty swallowing, difficulty swallowing foods, or to produce complications as the tumor spreads beyond the esophagus and grows into the surrounding organs, like the lungs or the major blood vessels that are sitting right behind the esophagus.

Q: What kinds of treatments are used to treat esophageal cancer?

A: This is a very serious and difficult cancer to treat, in part because of the location and in part because very often by the time it is diagnosed, the tumor is difficult to take out and has spread beyond the esophagus into the local tissues. Treatment to attempt to cure it would involve radical surgery with resection of the esophagus in an attempt to remove all of the tumor mass. Radiation may be used as well.

Q: Has the Surgeon General of the United States concluded that smoking is a cause of esophageal cancer?

A: Yes, there was a causal conclusion in 1979. Esophageal cancer was first addressed in 1971, and the report stated, "Epidemiological studies have demonstrated that cigarette smoking is associated with the development of cancer of the esophagus." If the Court looks at U.S. Exhibit 17181 (JS046E), the Court can see a summary of the Surgeon General's conclusions

with regard to this disease from 1971 to 2004, including the causal conclusion announced by IARC in 2002.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes esophageal cancer?

A: Yes, smoking causes esophageal cancer.

Q: Doctor, let's turn next to cancer of the pancreas. Could you use U.S. Exhibit 17103 (JS02.3) entitled, "Other Organs in the Abdominal Cavity" to describe that cancer to the Court?

A: As shown in that exhibit, the pancreas is the secretory organ that sits at the back of the abdomen. It is the organ that makes digestive enzymes and insulin. It can be the primary site for cancer. Cancers of the pancreas are often very difficult to find and diagnose, although with modern methods of imaging, the CAT scan and the MRI, physicians can do a much, much better job now.

Typically persons who develop this type of cancer have symptoms as the cancer grows and spreads beyond the pancreas; back pain, for example, is a very common symptom because

the cancer begins to involve the abdominal wall or to move towards the spinal cord. It can also narrow and block the passage of the bile out of the liver so some persons present with jaundice; that is, they've turned yellow from the backup of by-products from the liver and gall bladder.

Q: What treatments are used to treat cancer of the pancreas?

A: Unfortunately, most people who present with this usually have too advanced a cancer to be treated. For those who can be treated, the approach is very radical form of surgery involving removal of the pancreas or much of the pancreas, and some reconstruction of the bile duct, within the abdominal cavity.

Q: Has the Surgeon General of the United States concluded that smoking is a cause of cancers of the pancreas?

A: There was a causal conclusion in 2004. Pancreatic cancers were first addressed in 1972, and the report stated, "Epidemiological evidence demonstrates a significant association between cigarette smoking and cancers of the pancreas." If the Court looks at U.S. Exhibit 17182 (JS046F), the Court can see a summary of the Surgeon General's conclusions with regard to this disease from 1972 to 2004, including the causal conclusion announced by IARC in 1986.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be reliable a authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes cancers of the pancreas?

A: Yes, smoking causes pancreatic cancer.

Q: Doctor Samet, let's turn now to bladder cancer. Could you describe that disease for the Court?

A: The urinary bladder, of course, is situated at the bottom of the abdominal or cavity. This is, of course, where the urine is stored. Bladder cancers arise in the cells that line the bladder, and symptoms occur essentially when the tumor has become big enough to disturb the flow of urine to cause blockage or blood in the urine. The cancer may be diagnosed as it spreads beyond the bladder, perhaps causing pain or complications in other adjacent organs.

Q: What treatments are used to treat bladder cancer?

A: The treatment depends on the stage of the disease and how aggressive the disease is. For some of the lower-grade cancers it may be possible to use primarily local treatments. For the more radical or more aggressive types of cancer, typically treatment would require removal of the bladder and perhaps local removal of lymph nodes surrounding the bladder.

Q: You mentioned "radical treatment," would that involve surgery?

A: That would be surgical removal, yes.

Q: You also mentioned "local treatment." What do you mean by that?

A: By that I mean treatment of the cancer using methods such as laser or other local treatments actually applied to the bladder cancer without removing the bladder.

Q: Doctor, when did the Surgeon General of the United States first conclude that smoking is a cause of bladder cancer?

A: There was a causal conclusion in 1990. Bladder cancer was first addressed in 1972, and the report stated, "Epidemiological studies have demonstrated a significant association between cigarette smoking and cancer of the urinary bladder in both men and women. These studies demonstrate that the risk of developing bladder increases with inhalation and the number of cigarettes smoked." If the Court looks at U.S. Exhibit 17183 (JS046G), the Court can see a summary of the Surgeon General's conclusions with regard to this disease from 1972 to 2004.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes cancer of the bladder?

A: Yes, smoking causes cancer of the bladder.

Q: Doctor, the next cancer is kidney cancer. Could you describe that disease to the Court?

A: Okay. Of course the kidneys also sit in the back of the abdominal cavity, the right and left kidneys. There are several types of kidney cancer, cancers involving the body of the kidney itself, and then cancers in the structures that take the urine out of the kidney as it's formed and guide it to the bladder. These cancers can arise in both of these areas of the kidney.

Symptoms occur when the cancer has become big enough to cause problems locally: pain, blood in the urine, perhaps blockage of the flow of urine out of one of the kidneys; or from spread of the cancer beyond the kidney into tissues around the kidney, or at a distance. Kidney -- some types of kidney cancer tend to metastasize fairly early, so there might be metastasis to the lungs or perhaps to the brain.

Q: Doctor, what kinds of treatments are used to treat kidney cancer?

A: For those cancers that are found early enough, taking out the kidney would be the surgical approach.

Q: Are there other kinds of treatments?

A: Some forms of chemotherapy might be used with kidney cancer, but the approach to cure would be removal at an early stage, and then again palliative treatments might be necessary for those who cannot be cured.

Q: Doctor, when did the Surgeon General of the United States first conclude that smoking is a cause of kidney cancer?

A: As early as 1982, cigarette smoking was recognized as a contributory factor in the development of kidney cancer. There was a conclusion in 1982 stating this, with the corollary that "the term 'contributory factor' by no means excludes the possibility of a causal role for smoking in cancers of this site." In 2004, the Surgeon General concluded that the relationship between cigarette smoking and kidney cancer is, in fact, causal. If the Court looks at U.S. Exhibit 17184 (JS046H), the Court can see a summary of the Surgeon General's causal conclusions with regard to this disease from 1982 to 2004.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider the Surgeon General's conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Now you have testified that the Surgeon General recently reached a conclusion regarding kidney cancer. Has any other organization reached a causal conclusion regarding kidney cancer?

A: Yes. The International Agency for Research on Cancer in its 1986 report reached the conclusion that smoking caused one of the types of kidney cancer that I mentioned, the type that involves the tubes, the structures that collect the urine within the kidney and channel it out of the kidney. Also in the 1995 update of that IARC report by Sir Richard Doll, who chaired the IARC meeting, he concluded that the evidence was now sufficient that smoking was a cause of the other type of kidney cancer that I mentioned, that of the body of the kidney itself.

Q: Did you review these IARC reports as part of your investigation in this case?

A: Yes.

Q: Do these reports form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider these reports to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes cancer of the kidneys?

A: Yes, smoking causes cancer of the kidneys.

Q: Doctor Samet, has research been carried out on smoking and the leukemias?

A: Yes, a number of studies have addressed smoking and the leukemias. The leukemias are categorized in many ways, the most basic being acute and chronic, and occurring in childhood and adulthood. The most common type of leukemia in adults is acute myeloid leukemia. The 2004 Surgeon General's Report states that there were approximately 10,500 cases of acute myeloid leukemia among adults in 2003 in the United States; the second leading type, chronic lymphocytic leukemia, accounted for approximately 7300 cases in that year.

Q: Is there a biological basis for considering that smoking could cause acute leukemia?

A: Yes. Cigarette smoke is known to contain several agents which cause leukemia, often referred to as leukemogens. One of the most important of these leukemogens is benzene, a well-established occupational cause of acute leukemia. For cigarette smokers, substantial benzene exposure is received and, in fact, blood and breath benzene levels are far higher in smokers than in nonsmokers. One study, carried out by scientists at the U.S. Environmental Protection Agency, showed that 90% of benzene exposures to smokers come from their smoking. We may also all experience some benzene exposure from filling the gasoline tank of a motor vehicle. Tobacco smoke also contains radioactive isotopes, polonium-210 and lead-210, which are also potential contributors to leukemia causation in smokers.

Q: What have the studies on smoking and risk for leukemia shown?

A: There is now a substantial published scientific literature on smoking and leukemia, with over 20 epidemiological studies on this association. The studies are of both the case-control and cohort design. These studies generally show increased risk for acute leukemia, with relative risk estimates in the range of 1.3 to 1.5, comparing ever smokers to never smokers. A number of studies show increasing risk with increasing numbers of cigarettes per day.

Q: Has the Surgeon General or other any other public health organizations reached a conclusion with regard to smoking as a cause of acute or chronic leukemia?

A: Yes, if the Court looks at U.S. Exhibit 17189 (JS046L) the International Agency for Research on Cancer concluded that the evidence was sufficient to reach a causal conclusion on the association of cigarette smoking with myeloid leukemia in 2002. The 2004 U.S. Surgeon General's Report reached a similar conclusion, stating that the evidence is sufficient to reach a causal conclusion for smoking and acute myeloid leukemia.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider these conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes acute myeloid leukemia?

A: Yes, smoking causes acute myeloid leukemia.

Q: Doctor, has the Surgeon General or any another public health organization concluded that smoking causes stomach cancer?

A: Yes. There have been many epidemiological studies on smoking and stomach cancer. In fact, stomach cancer was once one of the most common cancers, but its rate of occurrence dropped steadily over the last century, a decline attributed to changing foods along with better food preservation. In fact, we now have strong evidence that a bacterium, *Helicobacter pylori* is likely an important cause. Researchers have hypothesized that the prevalence of *Helicobacter pylori* infection probably declined across the last century, contributing to the drop in stomach cancer.

Even as this knowledge was gained and the epidemiological characteristics of stomach cancer evolved, many studies showed an association of smoking with stomach cancer. The relative risk values were relatively modest, but this association was repeatedly noted in a number of studies carried out beginning in the 1950s and 1960s.

Q: Has the U.S. Surgeon General or any other public health organization reviewed the evidence?

A: Yes, U.S. Exhibit 17195 (JS046) summarizes the Surgeon General's causal conclusion. The 2004 Report of the Surgeon General addressed smoking and stomach cancer. The review of evidence identified nine cohort studies and 11 case-control studies. Based on the findings of these studies, as well as considerations of plausibility, the report concluded that cigarette smoking causes gastric cancer. In 2002, the International Agency for Research on Cancer also concluded that smoking causes gastric cancer.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, they do.

Q: Do you consider these conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes stomach cancer?

A: Yes, smoking causes stomach cancer.

Q: Doctor Samet, has cigarette smoking been assessed as a cause of cervical cancer?

A: Yes, cigarette smoking has been evaluated as a cause of this cancer, which tends to affect younger women. Research on smoking and cervical cancer now needs to take account of the identification of Human Papilloma Virus (HPV) as a necessary cause for this cancer to develop. In a remarkable breakthrough, we have learned over the last two decades that this sexually-transmitted virus is likely requisite for the development of cervical cancer.

Q: Given the role of HPV, can smoking also be a cause?

A: Yes, researchers have addressed whether women who have HPV infection are more likely to develop cervical cancer if they smoke. In cohort studies, women who smoke, along with a comparison group of nonsmokers, have been followed for the identification of abnormalities of the cervix indicative of early forms of cancer. While only a few such studies have been conducted, the findings are clear: smokers are at higher risk for malignancy of the cervix, once HPV infection has taken place.

Q: Has the Surgeon General reached a conclusion on smoking and cervical cancer?

A: Yes, if the Court looks at U.S. Exhibit 17194 (JS046), the Court will see that in the 2004 report, the Surgeon General concluded that smoking is a cause of cervical cancer. This conclusion is consistent with that reached by the International Agency for Research on Cancer in its 2002 report.

Q: Did you review these conclusions as part of your investigation in this case?

A: Yes.

Q: Do these conclusions form part of the basis of your opinions in this case?

A: Yes, it does.

Q: Do you consider these conclusions to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes cervical cancer?

A: Yes it does.

Q: Doctor, has the Surgeon General or IARC concluded that any other cancers can be caused by smoking?

A: Yes, if the Court looks at the summary of conclusions in U.S. Exhibit 17190 (JS046M), the Court will see that in its 2002 report, the International Agency for Research on Cancer stated that there is now sufficient evidence to judge the association between tobacco smoking and liver cancer as causal. The Surgeon General has not yet reached that conclusion.

Q: Did you review this conclusion as part of your investigation in this case?

A: Yes.

Q: Does this conclusion form part of the basis of your opinions in this case?

A: Yes, it does.

Q: Do you consider this conclusion to be a reliable authority in the published scientific literature?

A: I do.

Q: Based on your education, training, expertise in the science of smoking and health, do you have an opinion to a reasonable degree of scientific certainty whether cigarette smoking causes liver cancer?

A: Yes, smoking causes liver cancer.

Q: Doctor, what do we know about how smoking causes the cancers other than lung cancer?

A: There are really two types of cancers that the Court should consider, those like the larynx or the mouth and in part of the esophagus, where the smoke is coming directly in contact with the surfaces where the cancers will arise. So the larynx, the voice box and the mouth, just like the lung, would be sites where the smoke would be inhaled and the carcinogens in the tobacco smoke deposited on the surface.

The esophagus probably is exposed to the carcinogens in tobacco smoke almost the same way, because the materials that are cleared out of the lung, the mucus that's naturally cleared out of the lung, contains tobacco smoke carcinogens in it, and that material is actually swallowed. We all produce mucus as we cleanse our lungs, and that mucus simply rises up the trachea, it's propelled by little what are called cilia, these are little whip-like objects that move the mucus up the trachea out of the lung, and we simply swallow that. So the esophagus would be receiving this material as it is swallowed, so presumably, there is some direct contact there as well.

The second group of cancers involve organs that are distant from the lungs, like the bladder, the pancreas, the stomach and the kidney. The carcinogens that have now passed through the body would be excreted by the kidneys where exposure to the kidney would occur, and then the urine would be sitting in the bladder with its load of materials related to smoking, including carcinogens.

The pancreas is another glandular organism, it is an organ that makes enzymes, and receives exposure to carcinogens through the circulation of these materials in the blood. This material crosses through the membrane that lines the lung, the alveolar membrane surface, into the capillaries and then spreads throughout the body.

Q: Doctor Samet, please direct your attention back to U.S. Exhibit 17108 (JS008) titled "Known Carcinogens in Cigarette Smoke." Can you tell the Court what the exhibit is?

A: This is a listing of 62 carcinogens in tobacco smoke, known human or animal carcinogens in tobacco smoke that had been identified by IARC by 2002.

Q: Are the carcinogens on this particular exhibit the carcinogens that you were just referring to about carcinogens in smoke?

A: Well these are the carcinogens identified to date, yes. There may be others that have not yet been identified.

Q: Doctor, now that you have finished your conclusions with regard to smoking as causing COPD and cancer, let's turn now to coronary heart disease. What is coronary heart disease?

A: Coronary heart disease, which physicians call CHD or CAD (coronary artery disease), refers to diseases affecting the blood vessels of the heart. The heart is a muscle and like all muscles, it needs oxygen and nutrients to do its job. The coronary arteries bring the blood to the

muscles of the heart. CHD refers to the development of disease within these blood vessels and inadequate delivery of oxygen, sugar and other nutrients to the heart muscle itself.

Q: What are the symptoms of the disease?

A: The symptoms vary, but one very common consequence of CHD is heart attack. A heart attack, or myocardial infarction, occurs when the heart has not received enough oxygen and parts of the heart muscle have actually died. People more commonly refer to this kind of event as a "heart attack."

Other times there has not been enough oxygen delivered to the heart muscle on a temporary basis, and the heart muscle does not actually die, but pain occurs because not enough oxygen has been delivered; that condition is commonly referred to as angina. Angina is a result of the same problem, not enough oxygen getting to the heart muscle. Finally, some people just die suddenly from heart failure, referred to as sudden death, and physicians often think that is due to coronary heart disease and the effects on the heart of inadequate oxygen delivery.

Q: What is atherosclerosis?

A: Atherosclerosis refers to the development of plaque, a thickening of the lining of the arteries. The arteries are blood vessels or tubes that bring the blood to the body's organs, including the heart. Atherosclerotic plaques, refer to a type of thickening that includes some fat or cholesterol within it, as well as the development of scarring. These plaques can contribute to blocking the flow of blood into the heart muscle and are a site on which blood clots may form.

Q: Does atherosclerosis fall under the category of coronary heart disease?

A: Atherosclerosis is part of the process involved in producing CHD.

Q: Doctor Samet, what are the treatments for CHD?

A: There are many available. People who have coronary heart disease may take medications that reduce the work load on the heart in order to reduce strain on the heart muscle so that its oxygen needs are lessened. People with angina may be given medications that increase the circulation of blood in the heart. One common form of medicine that people use on an emergency basis when they are having pain is nitroglycerin. These are pills that patients with this disease put under their tongue and they produce some immediate increase in the blood flow into the heart.

For patients with more advanced disease or with more serious problems, or depending on the plaque and blockages within the heart, they may have an angioplasty. That procedure takes place in a hospital and involves placing a catheter, a small tube, within the coronary arteries, and there is a balloon on that tube that is inflated to open up the blockage. That is often done now because, using that approach, surgery under a general anesthetic can be avoided.

For some patients, surgery is required. They may have what is called coronary artery bypass grafting (CABG). In that type of treatment, a blood vessel is taken from somewhere else and actually used to bypass the area of blockage in the coronary artery. An alternative is to place a stent which maintains the blood vessel as open as possible. Stents are used increasingly.

These are some of the main forms of treatment.

Q: Based on your training and clinical experience, what effect, if any, does the patient being a smoker have on treatment?

A: Smokers who have CHD have poorer prognosis if they continue to smoke. They probably use medical care at a higher rate than those who quit.

Q: Did you conduct an investigation of the published scientific literature regarding whether smoking is a cause of coronary heart disease?

A: Yes, I did.

Q: Did you look at the Surgeon General's reports?

A: Yes, I did.

Q: Did you investigate whether coronary heart disease met the criteria for cause as set out by the Surgeon General?

A: Yes, I did.

Q: Let's talk about the first two criteria, consistency and strength. Do you have an exhibit that shows the relative risk for coronary heart disease associated with smoking?

A: Yes.

Q: Doctor Samet, directing your attention to U.S. Exhibit 17163 (JS070), entitled, "Relative Risk of CHD, Current Smokers versus Never Smokers: Men," are the studies that are depicted in this graph among the published scientific literature that you reviewed as part of your investigation in this case?

A: Yes, they are.

Q: What does this graph show?

A: Like U.S. Exhibit 17134 (JS032) regarding lung cancer relative risks, this graph shows the relative risks in different epidemiological studies for CHD in men, comparing current smokers to never smokers. The graph shows the results of a number of different studies done from the 1950's on. The risk for never smokers is by definition set to one and the Court can see the findings of all these studies showing the increased relative risk of CHD for men over almost fifty years.